

1. Document ID: US 20010041668 A1

L7: Entry 1 of 46

File: PGPB

Nov 15, 2001

PGPUB-DOCUMENT-NUMBER: 20010041668  
PGPUB-FILING-TYPE: new  
DOCUMENT-IDENTIFIER: US 20010041668 A1

TITLE: METHODS FOR MODULATING HEMATOPOIESIS AND  
VASCULAR GROWTH

PUBLICATION-DATE: November 15, 2001  
US-CL-CURRENT: 514/2; 435/7.2, 514/44

APPL-NO: 09/ 021660  
DATE FILED: February 10, 1998  
CONTINUED PROSECUTION APPLICATION: CPA

IN: BARON, MARGARET H., FARRINGTON, SARAH M.,  
BELAUSSOFF, MARIA

AB: This application pertains to methods and compositions that  
modulate proliferation  
and/or differentiation of undifferentiated mesodermally-derived cells so as  
to have an effect  
on at least one of vascular growth and hematopoiesis.

L7: Entry 1 of 46

File: PGPB

Nov 15, 2001

DOCUMENT-IDENTIFIER: US 20010041668 A1  
TITLE: METHODS FOR MODULATING HEMATOPOIESIS AND  
VASCULAR GROWTH

DRTX:  
[0036] FIG. 17 shows the results of a rescue experiment using null mutant  
embryonic stem cells (ES)  
and adding back recombinant BMP-4 to the culture. (A) and (C) shows  
wild type embryoid bodies that  
arise from embryonic stem cells isolated from a wild type mouse. In (B) the  
embryonic stem cells are  
homozygous BMP-4 deficient. and the embryoid bodies lack detectable  
blood formation. In (D), BMP-4  
protein is added to the embryoid bodies of (B) and blood formation is  
observed.

2. Document ID: US 6331612 B1

L7: Entry 2 of 46

File: USPT

Dec 18, 2001

US-PAT-NO: 6331612  
DOCUMENT-IDENTIFIER: US 6331612 B1  
TITLE: Bone morphogenic protein-16 (BMP-16) compositions  
DATE-ISSUED: December 18, 2001

US-CL-CURRENT: 530/350; 530/351

APPL-NO: 9/ 328775  
DATE FILED: June 9, 1999

PARENT-CASE:

This application is a divisional of U.S. Ser. No. 08/715,202 filed Sep. 18,  
1996, now U.S. Pat. No.  
5,965,403.

IN: Celeste; Anthony J., Murray; Beth L.

AB: Purified BMP-16 proteins and processes for producing them are  
disclosed. DNA  
molecules encoding the BMP-16 proteins are also disclosed. The proteins  
may be used in the  
treatment of bone, cartilage, other connective tissue defects and disorders,  
including tendon,  
ligament and meniscus, in wound healing and related tissue repair, as well  
as for treatment of  
disorders and defects to tissues which include epidermis, nerve, muscle,  
including cardiac  
muscle, and other tissues and wounds, and organs such as liver, lung,  
cardiac, pancreas and  
kidney tissue. The proteins may also be useful for the induction of growth  
and/or  
differentiation of undifferentiated embryonic and stem cells.

L7: Entry 2 of 46

File: USPT

Dec 18, 2001

DOCUMENT-IDENTIFIER: US 6331612 B1  
TITLE: Bone morphogenic protein-16 (BMP-16) compositions

BSPR:  
The BMP-16 DNA sequence (SEQ ID NO: 1) and amino acid sequence  
(SEQ ID NO: 2) are set forth in the  
Sequence Listings. BMP-16 proteins may be capable of inducing the  
formation of cartilage, bone, or  
other connective tissue, or combinations thereof. The cartilage and/or bone  
and/or other connective  
tissue formation activity in the rat bone formation assay described below.  
BMP-16 proteins may be  
further characterized by the ability to demonstrate effects upon the growth  
and/or differentiation  
of embryonic cells and/or stem cells. Thus, the proteins or compositions of  
the present invention  
may also be useful for treating cell populations, such as embryonic cells or  
stem cell populations,  
to enhance or enrich the growth and/or differentiation of the cells.

BSPR:  
It is expected that other species, particularly human, have DNA sequences  
homologous to human BMP-16  
protein. The invention, therefore, includes methods for obtaining the DNA  
sequences encoding human  
BMP-16 protein, the DNA sequences obtained by those methods, and the  
human protein encoded by those  
DNA sequences. This method entails utilizing the human BMP-16 protein  
nucleotide sequence or  
portions thereof to design probes to screen libraries for the corresponding  
gene from other species  
or coding sequences or fragments thereof from using standard techniques.  
Thus, the present invention  
may include DNA sequences from other species, which are homologous to  
human BMP-16 protein and can  
be obtained using the human BMP-16 sequence. The present invention may  
also include functional  
fragments of the human BMP-16 protein, and DNA sequences encoding  
such functional fragments, as well  
as functional fragments of other related proteins. The ability of such a  
fragment to function is  
determinable by assay of the protein in the biological assays described for  
the assay of the BMP-16  
protein. A DNA sequence encoding the complete mature human BMP-16  
protein (SEQ ID NO:1) and the  
corresponding amino acid sequence (SEQ ID NO:2) are set forth herein.  
The BMP-16 proteins of the  
present invention, such as human BMP-16, may be produced by culturing a

cell transformed with the correlating DNA sequence, such as the human BMP-16 DNA sequence, and recovering and purifying protein, such as BMP-16, from the culture medium. The purified expressed protein is substantially free from other proteinaceous materials with which it is co-produced, as well as from other contaminants. The recovered purified protein is contemplated to exhibit cartilage and/or bone and/or connective tissue formation activity. Thus, the proteins of the invention may be further characterized by the ability to demonstrate cartilage and/or bone and/or other connective tissue formation activity in the rat bone formation assay described below. BMP-16 proteins may be further characterized by the ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may also be characterized by their ability to enhance or enrich the growth and/or differentiation of the cells.

#### BSPR:

The purified proteins of the present inventions may be used to generate antibodies, either monoclonal or polyclonal, to human BMP-16 and/or other BMP-16-related proteins, using methods that are known in the art of antibody production. Thus, the present invention also includes antibodies to human BMP-16 and/or other related proteins. The antibodies may be useful for purification of BMP-16 and/or other BMP-16 related proteins, or for inhibiting or preventing the effects of BMP-16 related proteins. The BMP-16 protein and related proteins may be useful for inducing the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may also be useful for treating relatively undifferentiated cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation of the cells. The treated cell populations may be useful for implantation and for gene therapy applications.

#### BSPR:

The BMP-16 proteins recovered from the culture medium are purified by isolating them from other proteinaceous materials from which they are co-produced and from other contaminants present. BMP-16 proteins may be characterized by the ability to induce the formation of cartilage and/or bone and/or other connective tissue and other tissue repair and differentiation, for example, in the rat bone formation assay described below. In addition, BMP-16 proteins may be further characterized by their effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may be characterized by the embryonic stem cell assay described below.

#### DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)

and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

#### DEPR:

In order to assay the effects of the BMP-16 proteins of the present invention, it is possible to assay the growth and differentiation effects in vitro on a number of available embryonic stem cell lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection in Rockville, Md.

3. Document ID: US 6322786 B1

L7: Entry 3 of 46

File: USPT

Nov 27, 2001

US-PAT-NO: 6322786  
DOCUMENT-IDENTIFIER: US 6322786 B1  
TITLE: Method of producing bone-inducing agent  
DATE-ISSUED: November 27, 2001

US-CL-CURRENT: 424/115; 424/573, 435/366, 514/2, 514/21

APPL-NO: 8/ 799343  
DATE FILED: February 13, 1997

#### PARENT-CASE:

This application claims the benefit of U.S. provisional application No. 60/011,703, filed on Feb. 15, 1996.

IN: Anderson; H. C.

AB: The present invention provides methods to isolate and purify components required for bone-induction using extracts of Saos-2 cells or proteins released by Saos-2 cells into conditioned tissue culture medium. In addition, the present invention provides a method of augmenting bone growth locally comprising implanting the near osteoprogenitor cells the bone inducing agent isolated in the methods of the present invention, together with a mechanically suitable biodegradable carrier.

L7: Entry 3 of 46

File: USPT

Nov 27, 2001

DOCUMENT-IDENTIFIER: US 6322786 B1  
TITLE: Method of producing bone-inducing agent

#### DEPR:

Certain BMPs have been shown to stimulate the expression of osseous phenotypic traits by cultured marrow stromal osteoprogenitor cells (31). Also, preosteoblastic cell lines have been induced by BMPs to express alkaline phosphatase (ALP) and other molecular markers

of bone cell differentiation.

These include primary rat osteoblast cells by BMP-2 or BMP-3 (9,39,43,48), and W-20-17 or C3H, 10T1/2 pluripotent mouse mesenchymal stem cells (23,60). Exposure to purified extracts of Saos-2

cells or fractions derived from Saos-2 cell conditioned culture media is capable of stimulating osseous differentiation by one or more of these cells. Establishing a system of in vitro bone induction using the Saos-2 cell bone-inducing agent provides a more quantifiable bioassay method for testing the osteoinductivity of various fractions and isolates of bone inducing agent. Furthermore, such an in vitro assay is ideal to study the mechanism of osteoinduction under defined conditions at the cellular level, e.g., bone inducing agent receptors, method of signal transduction, etc.

4. Document ID: US 6294320 B1

L7: Entry 4 of 46

File: USPT

Sep 25, 2001

US-PAT-NO: 6294320

DOCUMENT-IDENTIFIER: US 6294320 B1

TITLE: Cell matrix plaques of initial bone formation

DATE-ISSUED: September 25, 2001

US-CL-CURRENT: 435/4; 435/343, 435/343.1, 530/388.7

APPL-NO: 9/ 454330

DATE FILED: December 3, 1999

PARENT-CASE:

The contents of Applicant's provisional application Ser. No. 60/110,878 filed Dec. 4, 1998 are hereby incorporated by reference.

IN: Hruska; Keith, Wozniak; Magdalena

AB: An isolated and essentially purified cell matrix plaque of initial bone formation comprising of .alpha..sub.v.beta..sub.3 integrin and rapid assays using such cell matrix plaques to measure potentials of factors, regimens or tissues for stimulation and/or inhibition of bone formation.

L7: Entry 4 of 46

File: USPT

Sep 25, 2001

DOCUMENT-IDENTIFIER: US 6294320 B1

TITLE: Cell matrix plaques of initial bone formation

DEPR:

Utilizing this discovery, a method of measuring new bone formation using a rapid in vitro assay has been developed. The method involves extracting bone marrow stromal cells from bone marrow cavities and growing them to semi-confluence; exposing the cells to a candidate medium or regimen for osteogenesis or inhibition of osteogenesis; determining the mineralization/development of bone plaque; and, optionally, comparing the mineralization/development of bone plaque generated using the

candidate medium or regimen with the mineralization/development of bone plaque using a preselected control such as bone morphogenetic factor-7 (BMP-7), also known as osteogenic factor-1 (OP-1).

DEPR:

Bone marrow stromal cells grown to semi-confluence and then exposed to osteogenic medium containing 10 mM of .beta.-glycerophosphate, 50 .mu.g/ml ascorbic acid and 40 ng/ml of osteogenic protein OP-1(32) also referred to as bone morphogenetic protein-7 (BMP-7), for 48 hours were defined as preosteoblasts. These preosteoblast cultures are characterized by alkaline phosphatase activity of 80,000 nmole pNPP/min./ .mu.g protein, osteopontin expression, absence of osteocalcin expression, and mineralization after 14 days in osteogenic media. For the purposes of this paper, bone marrow stromal cells exposed to OP-1-containing osteogenic medium for 14 days were defined as "mineralizing preosteoblasts" or osteoblasts. The osteoblast cultures are characterized by alkaline phosphatase activity of 60,000 nmole pNPP/min./ .mu.g protein, osteopontin expression, osteocalcin expression and mineralization of the extracellular matrix.

5. Document ID: US 6291206 B1

L7: Entry 5 of 46

File: USPT

Sep 18, 2001

US-PAT-NO: 6291206

DOCUMENT-IDENTIFIER: US 6291206 B1

TITLE: BMP receptor proteins

DATE-ISSUED: September 18, 2001

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 435/325, 536/23.1, 536/23.5, 536/23.51

APPL-NO: 8/ 123934

DATE FILED: September 17, 1993

IN: Wozney; John M., Celeste; Anthony J., Thies; R. Scott, Yamaji; Noboru

AB: Novel serine/threonine receptor proteins and BMP receptor proteins are disclosed, as well as DNA molecules encoding said proteins and methods of using the receptor proteins. Further disclosed are truncated BMP receptor proteins and molecules which act as ligands to said BMP receptor proteins.

L7: Entry 5 of 46

File: USPT

Sep 18, 2001

DOCUMENT-IDENTIFIER: US 6291206 B1

TITLE: BMP receptor proteins

DEPR:

Use of the W-20-17 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology,

130:1318 (1992)].

Specifically, W-20-17 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of

W-20-17 cells with certain BMP proteins results in (1) increased alkaline phosphatase production,

(2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While

(1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to

synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,

to date we have observed conversion of W-20-17 stromal cells to osteoblastlike cells only upon

treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20-17 cells

correlate with the in vivo bone forming activity known for BMPs.

6. Document ID: US 6287816 B1

L7: Entry 6 of 46

File: USPT

Sep 11, 2001

US-PAT-NO: 6287816

DOCUMENT-IDENTIFIER: US 6287816 B1

TITLE: BMP-9 compositions

DATE-ISSUED: September 11, 2001

US-CL-CURRENT: 435/69.4; 424/423, 424/426, 424/484, 435/252.3, 435/320.1, 435/325, 514/12, 530/399, 530/840, 536/23.51, 536/24.31, 930/120

APPL-NO: 8/ 254353

DATE FILED: June 6, 1994

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No.

08/050,132 filed Apr. 22, 1993 now U.S. Pat. No. 5,661,007 which is a continuation-in-part of U.S.

Ser. No. 07/720,590 filed Jun. 25, 1991, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY

APPL-NO

APPL-DATE

WO

PCT/US92/05374

June 25, 1992

IN: Rosen; Vicki A., Wozney; John M., Celeste; Anthony J., Thies; R. Scott, Song; Jeffrey R.

AB: Purified bone morphogenetic protein-9 (BMP-9) proteins and processes for producing them are disclosed. The proteins may be used in the treatment of bone and cartilage defects and in wound healing and related tissue repair.

L7: Entry 6 of 46

File: USPT

Sep 11, 2001

DOCUMENT-IDENTIFIER: US 6287816 B1

TITLE: BMP-9 compositions

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al., "Bone

Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and

Mineral Research 5(2):305 (1990); and R. S. Thies et al., "Recombinant Human Bone Morphogenetic

Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology, in press

(1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice

by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. BMP-2

treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of

PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2)

represent characteristics associated with the osteoblast phenotype, the ability to synthesize

osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we

have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with

BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the

in vivo bone forming activity known for BMPs.

7. Document ID: US 6261586 B1

L7: Entry 7 of 46

File: USPT

Jul 17, 2001

US-PAT-NO: 6261586

DOCUMENT-IDENTIFIER: US 6261586 B1

TITLE: Bone graft composites and spacers

DATE-ISSUED: July 17, 2001

US-CL-CURRENT: 424/423; 424/422, 424/426, 424/548, 424/549, 514/2, 523/115, 530/840, 606/61, 623/17.12

APPL-NO: 9/ 386560

DATE FILED: August 31, 1999

PARENT-CASE:

This application is a continuation of applicants' U.S. patent application Ser. No. 08/873,276, filed

Jun. 11, 1997, now U.S. Pat. No. 5,972,368.

IN: McKay; William F.

AB: A bone graft substitute including a composition of natural selectively deactivated

bone material which has been processed to remove associated non-collagenous bone proteins, said

bone material containing native collagen materials and naturally associated bone minerals and

substantially free from native non-collagenous protein, and a therapeutically effective amount

to stimulate bone growth of a bone growth factor in a pharmaceutically acceptable carrier in

synergistic combination with said bone material. Spacers composed of the bone graft substitute

composition methods for using the spacers are also provided.

L7: Entry 7 of 46

File: USPT

Jul 17, 2001

DOCUMENT-IDENTIFIER: US 6261586 B1  
TITLE: Bone graft composites and spacers

DEPR:

This invention provides the further advantage of exploiting the discovery that bone mineral is an excellent carrier for osteogenic factors such as bone morphogenic proteins. Hydroxyapatite which is very similar in chemical composition to the mineral in cortical bone is an osteogenic factor-binding agent which controls the rate of delivery of certain proteins to the fusion site. Calcium phosphate compositions such as hydroxyapatite are thought to bind bone morphogenic proteins and prevent BMP from prematurely dissipating from the spacer before fusion can occur. It is further believed that retention of the BMP by the agent permits the protein to initiate the transformation of mesenchymal stem cells into bone producing cells or osteoblasts within the device at a rate that is conducive to complete and rapid bone formation and ultimately, fusion across the disc space. The spacers of this invention have the advantage of including a load bearing member composed of selectively deactivated bone which naturally binds and provides controlled delivery of osteogenic factors such as bone morphogenic proteins.

8. Document ID: US 6251671 B1

L7: Entry 8 of 46

File: USPT

Jun 26, 2001

US-PAT-NO: 6251671  
DOCUMENT-IDENTIFIER: US 6251671 B1  
TITLE: Compositions and methods of making embryonic stem cells  
DATE-ISSUED: June 26, 2001

US-CL-CURRENT: 435/384; 435/385, 435/386, 435/387

APPL-NO: 8/ 808346  
DATE FILED: February 28, 1997

PARENT-CASE:

This Application claims the benefit of U.S. Provisional applications 60/012386 Filed Feb. 28, 1996 and 60/012,384 filed Feb. 28, 1996.

IN: Hogan; Brigid L. M., Zhao; Guang-Quan

AB: The invention relates to cell proliferation, cell differentiation, male infertility, male fertility and to compositions and methods involved therein. Also methods of culturing spermatogonial stem cells with bone morphogenetic protein 8 are disclosed.

L7: Entry 8 of 46

File: USPT

Jun 26, 2001

DOCUMENT-IDENTIFIER: US 6251671 B1  
TITLE: Compositions and methods of making embryonic stem cells

BSPR:

Mutations in other Bmp genes have been generated by homologous recombination in embryonic stem cells. For example, Bmp7 homozygous null mutant mice die shortly after birth with major defects in eye, kidney and limb development (Dudley et al., 1995, Genes Dev. 9:2795-2807; Luo et al., 1995, Genes Dev. 9:2808-2820). Most Bmp4 homozygous mutant embryos die around the time of gastrulation and many exhibit a deficiency in extraembryonic and posterior/ventral mesoderm (Winnier et al., 1995, Genes Dev. 9:2105-2116), a finding consistent with the effect of BMP4 on mesoderm patterning in Xenopus embryos (Jones et al., 1992, Development 115:639-647; Graff et al., 1994, Cell 79:169-179; Harland, 1994, Proc. Natl. Acad. Sci. USA 91:10243-10246). Mutations have also been described in other members of the BMP superfamily, including mouse nodal, and Gdf5 (brachypodism) (Zhou et al., 1993, Nature 361:543-547; Conlon et al., 1994, Development 120:1919-1928; Storm et al., 1994, Nature 368:639-643).

BSPR:

Also included in the invention is a method of differentiating mammalian spermatogonial stem cells, comprising culturing spermatogonial stem cells in the presence of BMP, or a biologically active fragment or an agonist thereof, to effect differentiation of the cells.

9. Document ID: US 6190880 B1

L7: Entry 9 of 46

File: USPT

Feb 20, 2001

US-PAT-NO: 6190880  
DOCUMENT-IDENTIFIER: US 6190880 B1  
TITLE: Recombinant bone morphogenetic protein heterodimers, compositions and methods of use  
DATE-ISSUED: February 20, 2001

US-CL-CURRENT: 435/69.1; 435/252.3, 435/252.33, 435/255.1, 435/320.1, 435/325, 435/70.2, 530/350, 530/399, 536/23.5

APPL-NO: 8/ 469411  
DATE FILED: June 6, 1995

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation of application Ser. No. 07/989,847, filed Nov. 27, 1992, now U.S. Pat. No. 5,866,364 which is a continuation-in-part of U.S. Ser. No. 07/864,692 filed Apr. 7, 1992, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/787,496 filed Nov. 4, 1991, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:  
COUNTRY

APPL-NO

APPL-DATE

WO

PCT/US92/09430

November 2, 1992

IN: Israel; David, Wolfman; Neil M.

AB: The present invention relates to a methods for producing recombinant heterodimeric BMP proteins useful in the field of treating bone defects, healing bone injury and in wound healing in general. The invention also relates to the recombinant heterodimers and compositions containing them.

L7: Entry 9 of 46

File: USPT

Feb 20, 2001

DOCUMENT-IDENTIFIER: US 6190880 B1  
TITLE: Recombinant bone morphogenetic protein heterodimers, compositions and methods of use

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al, "Bone Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and Mineral Research, 5(2) :305 (1990); and R. S. Thies et al, "Recombinant Human Bone Morphogenetic Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology, in press (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. BMP-2 treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPS.

10. Document ID: US 6179872 B1

L7: Entry 10 of 46

File: USPT

Jan 30, 2001

US-PAT-NO: 6179872  
DOCUMENT-IDENTIFIER: US 6179872 B1  
TITLE: Biopolymer matt for use in tissue repair and reconstruction  
DATE-ISSUED: January 30, 2001

US-CL-CURRENT: 623/11.11; 428/304.4, 442/123, 530/354, 530/356

APPL-NO: 9/ 042549  
DATE FILED: March 17, 1998

IN: Bell; Eugene, Sioussat; Tracy M., Begley; Michael J.

AB: Biopolymer matt, biopolymer matt composites, biopolymer matt

compositions, and methods of preparing the matt and composite matts are described. Also described are biocompatible constructs which include extracellular matrix macromolecules and methods of preparing these constructs. The matt, matt compositions and biocompatible constructs of the invention can be used in tissue repair and reconstruction.

L7: Entry 10 of 46

File: USPT

Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6179872 B1  
TITLE: Biopolymer matt for use in tissue repair and reconstruction

DEPR:

The term "growth factors" is art recognized and is intended to include, but is not limited to, one or more of platelet derived growth factors (PDGF), e.g., PDGF AA, PDGF BB; insulin-like growth factors (IGF), e.g., IGF-I, IGF-II; fibroblast growth factors (FGF), e.g., acidic FGF, basic FGF, .beta.-endothelial cell growth factor, FGF 4, FGF 5, FGF 6, FGF 7, FGF 8, and FGF 9; transforming growth factors (TGF), e.g., TGF-P1, TGF-.beta.1.2, TGF-.beta.2, TGF-.beta.3, TGF-.beta.5; bone morphogenic proteins (BMP), e.g., BMP 1, BMP 2, BMP 3, BMP 4; vascular endothelial growth factors (VEGF), e.g., VEGF, placenta growth factor; epidermal growth factors (EGF), e.g., EGF, amphiregulin, betacellulin, heparin binding EGF; interleukins, e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14; colony stimulating factors (CSF), e.g., CSF-G, CSF-GM, CSF-M; nerve growth factor (NGF); stem cell factor; hepatocyte growth factor, and ciliary neurotrophic factor. The term encompasses presently unknown growth factors that may be discovered in the future, since their characterization as a growth factor will be readily determinable by persons skilled in the art.

DEPR:

Growth factors necessary for cell growth are attached to structural elements of the extracellular matrix. The structural elements include proteins, e.g., collagen and elastin, glycoproteins, proteoglycans and glycosaminoglycans. The growth factors, originally produced and secreted by cells, bind to the extracellular matrix and regulate cell behavior in a number of ways. These factors include, but are not limited to, one or more of platelet derived growth factors (PDGF), e.g., PDGF AA, PDGF BB; insulin-like growth factors (IGF), e.g., IGF-I, IGF-II; fibroblast growth factors (FGF), e.g., acidic FGF, basic FGF, .beta.-endothelial cell growth factor, FGF 4, FGF 5, FGF 6, FGF 7, FGF 8, and FGF 9; transforming growth factors (TGF), e.g., TGF-.beta.1, TGF-.beta.1.2, TGF-.beta.2, TGF-.beta.3, TGF-.beta.5; bone morphogenic proteins (BMP), e.g., BMP 1, BMP 2, BMP 3, BMP 4; vascular endothelial growth factors (VEGF), e.g., VEGF, placenta growth factor; epidermal growth factors (EGF), e.g., EGF, amphiregulin, betacellulin, heparin binding EGF; interleukins, e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14; colony stimulating factors (CSF), e.g., CSF-G, CSF-GM, CSF-M; nerve growth factor (NGF); stem cell factor; hepatocyte growth factor, and ciliary neurotrophic factor. Adams et al., "Regulation of Development and Differentiation by the Extracellular Matrix" Development Vol. 117, p. 1183-1198 (1993) (hereinafter "Adams et al.") and Kreis et al. editors of the book

entitled "Guidebook to the Extracellular Matrix and Adhesion Proteins," Oxford University Press (1993) (hereinafter "Kreis et al.") describe extracellular matrix components that regulate differentiation and development.

Further, Adams et al. disclose examples of association of growth factors with extracellular matrix proteins and that the extracellular matrix is an important part of the micro-environment and, in collaboration with growth factors, plays a central role in regulating differentiation and development. The teachings of Adams et al. and Kreis et al. are incorporated herein by reference.

11. Document ID: US 6165748 A

L7: Entry 11 of 46

File: USPT

Dec 26, 2000

US-PAT-NO: 6165748

DOCUMENT-IDENTIFIER: US 6165748 A

TITLE: Frazzled nucleotide sequences and expression products

DATE-ISSUED: December 26, 2000

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 435/325, 530/300, 530/350, 536/23.1, 536/23.5

APPL-NO: 8/ 893654

DATE FILED: July 11, 1997

IN: Racie; Lisa, Lavallie; Edward, Paulsen; Janet, Sive; Hazel, Sun; Benjamin

AB: Purified Frazzled proteins, including WG67-16, WG67-19 and WA628, and processes for producing them are disclosed. DNA molecules encoding the Frazzled proteins, including WG67-16, WG67-19 and WA628, are also disclosed. The proteins may be used in modulating the binding of

Wnt genes to their receptor. They are useful in the modulation of cellular formation, growth, differentiation, proliferation and/or maintenance of a variety of adult and embryonic tissues and organs.

L7: Entry 11 of 46

File: USPT

Dec 26, 2000

DOCUMENT-IDENTIFIER: US 6165748 A

TITLE: Frazzled nucleotide sequences and expression products

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with an osteogenic protein, such as a BMP protein (Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)). Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline

phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

12. Document ID: US 6083690 A

L7: Entry 12 of 46

File: USPT

Jul 4, 2000

US-PAT-NO: 6083690

DOCUMENT-IDENTIFIER: US 6083690 A

TITLE: Methods and compositions for identifying osteogenic agents

DATE-ISSUED: July 4, 2000

US-CL-CURRENT: 435/6; 435/29, 435/320.1, 435/325, 435/375, 435/4, 435/455, 536/23.1, 536/24.1

APPL-NO: 8/ 458434

DATE FILED: June 2, 1995

IN: Harris; Stephen E., Mundy; Gregory R., Ghosh-Choudhury; Nandini, Feng; Jian Q.

AB: Methods and compositions for identifying osteogenic agents are disclosed, wherein a bone morphogenetic protein promoter is utilized in an assay system to modulate the production of an assayable product of a reporter gene.

L7: Entry 12 of 46

File: USPT

Jul 4, 2000

DOCUMENT-IDENTIFIER: US 6083690 A

TITLE: Methods and compositions for identifying osteogenic agents

DEPR:

Several BMP-4 cDNAs were sequenced from prostate cancer cell line PC-3 and from primary FRC cells.

Four independent FRC cell BMP-4 cDNAs all contained exon 1A. However, the human prostate carcinoma cell line (PC-3) cDNA contained an apparently unique exon 1B sequence spliced to exon 2 (Chen et al, 1993). A double-stranded oligonucleotide probe (70 bp) to exon 1B was synthesized based on the human

PC-3 exon 1B sequence. This exon 1B probe was then used to identify the exon 1B region in the mouse genomic BMP-4 clone. The candidate exon 1B is 1696 bp downstream from the 3' end of exon 1A.

DEPR:

To analyze the activity of the BMP-2 promoter in cell types not expressing BMP-2 mRNA, BMP-2 promoter constructs were transfected into CV-1 cells (monkey kidney cells). The BMP-2 promoter activity was found to be very low for all constructs. This suggests that this region of the BMP-2

promoter is functional only in cells such as primary fetal rat calvarial osteoblasts, HeLa and ROS

172.8 that express endogenous BMP-2 mRNA (Anderson & Coulter 1968). CV-1 cells do not express BMP-2

mRNA. The BMP-2 promoter is likely active in other cell types that express BMP-2, such as prostate

cells and chondrocytes, although regulation of transcription may be different in these cells.

13. Document ID: US 6080779 A

L7: Entry 13 of 46

File: USPT

Jun 27, 2000

US-PAT-NO: 6080779

DOCUMENT-IDENTIFIER: US 6080779 A

TITLE: Compositions and methods for stimulating bone growth

DATE-ISSUED: June 27, 2000

US-CL-CURRENT: 514/451; 514/141, 514/185, 514/700

APPL-NO: 9/ 096957

DATE FILED: June 12, 1998

PARENT-CASE:

This application claims priority under 35 USC 119 from provisional application Ser. No. 60/032,893

filed Dec. 13, 1996. It is also a continuation-in-part of U.S. Ser. No. 08/989,862 filed Dec. 12,

1997 claiming benefit under 35 USC 120. The entire contents of these documents are incorporated herein by reference.

IN: Gasper; Shirley R., West; Robert R., Martinez; Theresa, Robbins; Kirk G., McKernan; Patricia A., Baidur; Nand, Labroo; Virender M., Mundy; Gregory R.

AB: Compounds of the formula ##STR1## wherein X in each of formulas (1) and (2)

represents a substituted or unsubstituted alkylene, alkenylene, or alkynylene linker of 2-6 C;

Y represents one or more carbocyclic or heterocyclic rings; when two or more rings are present

in Y, they may optionally be fused; and, R' represents a cation, H or a substituted or

unsubstituted alkyl group of 1-6 C; and, the dotted lines represent optional .pi.-bonds,,

promote bone formation and are thus useful in treating osteoporosis, bone fracture or

deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic

bone disease, osteolytic bone disease, post-plastic surgery,

post-prosthetic joint surgery, and

post-dental implantation. These compounds can be used in combination with other bone

growth-promoting compounds and/or estrogens and/or bisphosphonates for this purpose.

L7: Entry 13 of 46

File: USPT

Jun 27, 2000

DOCUMENT-IDENTIFIER: US 6080779 A

TITLE: Compositions and methods for stimulating bone growth

ORPL:

Rickard, D.J. et al., "Induction of Rapid Osteoblast Differentiation in Rat Bone Marrow Stromal Cell

Cultures by Dexamethasone and BMP-2," Developmental Biology (1994) 161:218-228.

14. Document ID: US 6077987 A

L7: Entry 14 of 46

File: USPT

Jun 20, 2000

US-PAT-NO: 6077987

DOCUMENT-IDENTIFIER: US 6077987 A

TITLE: Genetic engineering of cells to enhance healing and tissue regeneration

DATE-ISSUED: June 20, 2000

US-CL-CURRENT: 623/23.72; 424/422, 424/423, 424/93.21, 623/23.57, 623/23.6

APPL-NO: 8/ 923718

DATE FILED: September 4, 1997

IN: Breitbart; Arnold S., Grande; Daniel S., Mason; James M.

AB: A method for enhancing and/or increasing the efficiency of repair of tissues,

primarily bone or cartilage, using genetically engineered cells has been developed. In the

preferred embodiment, mesenchymal stem cells are isolated from periosteum tissue, and

transfected with the gene encoding a growth factor for the particular cell type to be repaired.

For example, for repair of bone, a gene (or genes) encoding bone morphogenic protein is

transfected into periosteal cells. The transfected periosteal cells then express the bone

morphogenic protein in culture to promote bone repair as a function of the expressed bone

morphogenic protein. Cells can be transfected using any appropriate means, including viral

vectors, as shown by the example, chemical transfectants, or physico-mechanical methods such as

electroporation and direct diffusion of DNA. Genes can encode any useful protein, for example,

a specific growth factor, morphogenesis factor, a structural protein, or a cytokine which

enhances the temporal sequence of wound repair, alters the rate of proliferation, increases the

metabolic synthesis of extracellular matrix proteins, or directs phenotypic expression in

endogenous cell populations. Representative genes encoding proteins include bone growth factor

genes, cartilage growth factor genes, nerve growth factor genes, and general growth factors

important in wound healing, such as platelet-derived growth factor (PDGF), vascular endothelial

growth factor (VEGF), insulin-like growth factor (IGF-1), epidermal growth factor (EGF), basic

fibroblast growth factor (FGF), endothelial derived growth supplement.

L7: Entry 14 of 46

File: USPT

Jun 20, 2000

DOCUMENT-IDENTIFIER: US 6077987 A

TITLE: Genetic engineering of cells to enhance healing and tissue regeneration



BSPR:  
Preferred examples for bone repair and/or treatment of osteoporosis uses periosteal or other mesenchymal stem cells or osteocytes/osteoblasts transfected with bone growth factor genes such as bone morphogenetic protein (BMP) family genes, including BMP 2-15; for cartilage repair uses periosteal cells or chondrocytes transfected with cartilage growth factor genes such as transforming growth factor-.beta. (TGF-.beta.) and cartilage growth factor (CGF); for wound healing uses dermal or epidermal cells transfected with growth factor genes such as platelet derived growth factor (PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), fibroblast growth factor (FGF), endothelial derived growth supplement (EDGS), or insulin-like growth factor (IGF); for nerve repair (central and/or peripheral) uses neural cells and neural support cells transfected with nerve growth factor (NGF) gene.

15. Document ID: US 6034229 A

L7: Entry 15 of 46

File: USPT

Mar 7, 2000

US-PAT-NO: 6034229  
DOCUMENT-IDENTIFIER: US 6034229 A  
TITLE: BMP-15 compositions  
DATE-ISSUED: March 7, 2000

US-CL-CURRENT: 536/23.5

APPL-NO: 8/ 982987  
DATE FILED: December 2, 1997

PARENT-CASE:

This application is a continuation of U.S. Ser. No. 08/798,665, filed Feb. 11, 1997 and now, which application is a divisional of U.S. Ser. No. 08/446,924, filed May 18, 1995 and now issued as U.S. Pat. No. 5,635,372.

IN: Celeste; Anthony J., Dube; Jennifer L., Lyons; Karen M., Hogan; Brigid

AB: Purified BMP-15-related proteins and processes for producing them are disclosed. DNA molecules encoding the BMP-15-related proteins are also disclosed. The proteins may be used in the treatment of bone and cartilage and/or other connective tissue defects and in wound healing and related tissue repair.

L7: Entry 15 of 46

File: USPT

Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034229 A  
TITLE: BMP-15 compositions

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein

[Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].

Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

16. Document ID: US 6034062 A

L7: Entry 16 of 46

File: USPT

Mar 7, 2000

US-PAT-NO: 6034062  
DOCUMENT-IDENTIFIER: US 6034062 A  
TITLE: Bone morphogenetic protein (BMP)-9 compositions and their uses  
DATE-ISSUED: March 7, 2000

US-CL-CURRENT: 514/12; 530/350, 530/399, 930/120

APPL-NO: 8/ 815652  
DATE FILED: March 13, 1997

IN: Thies; R. Scott, Song; Jeffrey J.

AB: Purified Bone Morphogenetic Protein (BMP)-9 proteins and processes for producing them are disclosed. The proteins may be used in the treatment of bone and cartilage defects and in wound healing and related tissue repair, and in hepatic growth and function.

L7: Entry 16 of 46

File: USPT

Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034062 A  
TITLE: Bone morphogenetic protein (BMP)-9 compositions and their uses

DEPR:

Human BMP-9 may be produced by culturing a cell transformed with a DNA sequence comprising nucleotide #124 to #453 as shown in SEQ ID NO:8 and recovering and purifying from the culture medium a protein characterized by the amino acid sequence of SEQ ID NO:9 from amino acid #1 to amino acid #110 substantially free from other proteinaceous materials with which it is co-produced. For production in mammalian cells, the DNA sequence further comprises a DNA sequence encoding a suitable propeptide 5' to and lined in frame to the nucleotide sequence encoding the mature BMP-9-related polypeptide. The propeptide may be the native BMP-9-related propeptide,

or may be a propeptide from another protein of the TGF- $\beta$  superfamily. BMP-9 proteins may be characterized by the ability to induce the formation of cartilage. BMP-9 proteins may be further characterized by the ability to induce the formation of bone. BMP-9 proteins may be further characterized by the ability to demonstrate cartilage and/or bone formation activity in the rat bone formation assay described below. BMP-9 proteins may be further characterized by the ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells. The proteins or compositions of the present invention may also be useful for treating cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation of the cells.

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al., "Bone Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", *Journal of Bone and Mineral Research* 5(2):305 (1990); and R. S. Thies et al., "Recombinant Human Bone Morphogenetic Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", *Endocrinology*, 130(3):1318-1324 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. BMP-2 treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

DEPR:

To determine if this proliferative effect of BMP-9 was unique to the HepG2 liver tumor cell line, primary rat hepatocytes were tested for effects of BMP-9 on .sup.3 H-thymidine incorporated as shown in FIG. 4. BMP-9 stimulated .sup.3 H-thymidine incorporation in primary hepatocytes, although not as markedly as EGF. This stimulatory effect is cell density-dependent in primary rat hepatocytes. While subconfluent cells exhibited a stimulation in response to BMP-9, confluent primary hepatocytes did not. As indicated in FIG. 4, in contrast to rhBMP-9, TGF- $\beta$ .1 was inhibitory, not stimulatory on primary rat hepatocytes.

DEPR:

In order to assay the effects of the BMP-9 proteins of the present invention, it is possible to assay the growth and differentiation effects in vitro on a number of available embryonic stem cell lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection in Rockville, Md.

17. Document ID: US 6034061 A

L7: Entry 17 of 46

File: USPT

Mar 7, 2000

US-PAT-NO: 6034061  
DOCUMENT-IDENTIFIER: US 6034061 A  
TITLE: BMP-9 compositions  
DATE-ISSUED: March 7, 2000

US-CL-CURRENT: 514/12; 424/423, 424/426, 435/69.4, 514/2, 530/399, 530/840, 536/23.51, 536/24.31, 930/120

APPL-NO: 8/ 750222  
DATE FILED: December 4, 1996

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS This application is a 371 of PCT/US95/07084, filed Jun. 5, 1995; which is a continuation of U.S. Ser. No. 08/254,353, filed Jun. 6, 1994; which is a continuation of U.S. Ser. No. 08/050,132, filed Apr. 22, 1993 now abandoned (U.S. Pat. No. 5,661,007); which is a continuation-in-part of PCT/US92/05374 filed Jun. 25, 1992; which is a continuation-in-part of Ser. No. 07/720,590, filed Jun. 25, 1991, now abandoned.

IN: Rosen; Vicki A., Wozney; John M., Celeste; Anthony J., Thies; Scott R., Song; Jeffrey R.

AB: Purified Bone Morphogenetic Protein (BMP)-9 proteins and processes for producing them are disclosed. The proteins may be used in the treatment of bone and cartilage defects and in wound healing and related tissue repair, and in hepatic growth and function.

L7: Entry 17 of 46

File: USPT

Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034061 A  
TITLE: BMP-9 compositions

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al., "Bone Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", *Journal of Bone and Mineral Research* 5(2):305 (1990); and R. S. Thies et al., "Recombinant Human Bone Morphogenetic Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", *Endocrinology*, in press (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, MA. BMP-2 treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated

W-20 cells correlate with the  
in vivo bone forming activity known for BMPs.

**DEPR:**

To determine if this proliferative effect of BMP-9 was unique to the HepG2 liver tumor cell line, primary rat hepatocytes were tested for effects of BMP-9 on .sup.3 H-thymidine incorporated as shown in FIG. 7. BMP-9 stimulated .sup.3 h-thymidine incorporation in primary hepatocytes, although not as markedly as EGF. This stimulatory effect is cell density-dependent in primary rat hepatocytes. While subconfluent cells exhibited a stimulation in response to BMP-9, confluent primary hepatocytes did not. As indicated in FIG. 7, in contrast to rhBMP-9, TGF-.beta.1 was inhibitory, not stimulatory on primary rat hepatocytes.

18. Document ID: US 6027917 A

L7: Entry 18 of 46

Title: USPT

Feb 22, 2000

US-PAT-NO: 6027917

DOCUMENT-IDENTIFIER: US 6027917 A

TITLE: Bone morphogenetic protein (BMP)-17 and BMP-18 compositions

DATE-ISSUED: February 22, 2000

US-CL-CURRENT: 435/69.1; 435/252.3, 435/325, 536/23.5, 536/23.51

APPL-NO: 8/ 987904

DATE FILED: December 10, 1997

IN: Celeste; Anthony J., Murray; Beth L.

**AB:** Purified BMP-17 and BMP-18 proteins and processes for producing them are disclosed.

DNA molecules encoding the BMP-17 and BMP-18 proteins are also disclosed. The proteins may be used in the treatment of bone, cartilage, other connective tissue defects and disorders, including tendon, ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells.

L7: Entry 18 of 46

Title: USPT

Feb 22, 2000

DOCUMENT-IDENTIFIER: US 6027917 A

TITLE: Bone morphogenetic protein (BMP)-17 and BMP-18 compositions

**BSPR:**

The BMP-17 (SEQ ID NO: 1) and BMP-18 (SEQ ID NO: 3) DNA sequences and amino acid sequences (SEQ ID NO: 2 and 4, respectively) are set forth in the Sequence Listings. BMP-17 and BMP-18 proteins may be capable of inducing the formation of cartilage, bone, or other connective

tissue, or combinations

thereof. The cartilage and/or bone and/or other connective tissue formation activity in the rat bone

formation assay described below. BMP-17 and BMP-18 proteins may be further characterized by the

ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem

cells. Thus, the proteins or compositions of the present invention may also be useful for treating

cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth

and/or differentiation of the cells. Alternatively, the proteins or compositions of the present

invention may also be useful for maintenance of a cell population, including differentiated cell

populations, for example, neuronal cells, epithelial cells, dendritic cells, chondrocytes,

osteocytes, muscle cells or cells of other differentiated phenotypes.

**BSPR:**

It is expected that other species, particularly human, have DNA sequences homologous to human BMP-17

and BMP-18 protein. The invention, therefore, includes methods for obtaining the DNA sequences

encoding human BMP-17 and BMP-18 proteins, the DNA sequences obtained by those methods, and the

human proteins encoded by those DNA sequences. This method entails utilizing the human BMP-17 and

BMP-18 nucleotide sequences or portions thereof to design probes to screen libraries for the

corresponding gene from other species or coding sequences or fragments thereof from using standard

techniques. Thus, the present invention may include DNA sequences from other species, which are

homologous to human BMP-17 and BMP-18 proteins and can be obtained using the human BMP-17 and/or

BMP-18 sequences. The present invention may also include functional fragments of the human BMP-17

and BMP-18 proteins, and DNA sequences encoding such functional fragments, as well as functional

fragments of other related proteins. The ability of such a fragment to function is determinable by

assay of the protein in the biological assays described for the assay of the BMP-17 and BMP-18

proteins. DNA sequences encoding the complete mature human BMP-17 (SEQ ID NO: 1) and BMP-18 protein

(SEQ ID NO:3) and the corresponding amino acid sequences (SEQ ID NO:2 and 4, respectively) are set

forth herein. The BMP-17 and BMP-18 proteins of the present invention, such as human BMP-17 and

BMP-18, may be produced by culturing a cell transformed with the correlating DNA sequence, such as

the human BMP-17 and BMP-18 DNA sequence, and recovering and purifying protein, such as BMP-17 or

BMP-18, from the culture medium. The purified expressed protein is substantially free from other

proteinaceous materials with which it is co-produced, as well as from other contaminants. The

recovered purified protein is contemplated to exhibit cartilage and/or bone and/or connective tissue

formation activity. Thus, the proteins of the invention may be further characterized by the ability

to demonstrate cartilage and/or bone and/or other connective tissue formation activity in the rat

bone formation assay described below. BMP-17 and BMP-18 proteins may be further characterized by the

ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem

cells. Thus, the proteins or compositions of the present invention may also be characterized by

their ability to enhance or enrich the growth and/or differentiation of the cells.

**BSPR:**

The purified proteins of the present inventions may be used to generate antibodies, either

monoclonal or polyclonal, to human BMP-17 and/or BMP-18 and/or other BMP-17 and/or BMP-18-related

proteins, using methods that are known in the art of antibody production. Thus, the present invention also includes antibodies to human BMP-17 and/or BMP-18 and/or other related proteins. The antibodies may be useful for purification of BMP-17 and/or BMP-18 and/or other BMP-17 and/or BMP-18 related proteins, or for inhibiting or preventing the effects of BMP-17 and/or BMP-18 related proteins. The BMP-17 and/or BMP-18 protein and related proteins may be useful for inducing the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may also be useful for treating relatively undifferentiated cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation of the cells. The treated cell populations may be useful for implantation and for gene therapy applications.

**BSPR:**

The BMP-17 or BMP-18 proteins recovered from the culture medium are purified by isolating them from other proteinaceous materials from which they are co-produced and from other contaminants present. BMP-17 or BMP-18 proteins may be characterized by the ability to induce the formation of cartilage and/or bone and/or other connective tissue and other tissue repair and differentiation, for example, in the rat bone formation assay described below. In addition, BMP-17 or BMP-18 proteins may be further characterized by their effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may be characterized by the embryonic stem cell assay described below.

**DEPR:**

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, MA. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

**DEPR:**

In order to assay the effects of the BMP-17 and BMP-18 proteins of the present invention, it is possible to assay the growth and differentiation effects in vitro on a number of available embryonic stem cell lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection in Rockville, Md.

19. Document ID: US 6022887 A

L7: Entry 19 of 46

File: USPT

Feb 8, 2000

US-PAT-NO: 6022887  
DOCUMENT-IDENTIFIER: US 6022887 A  
TITLE: Compositions and methods for stimulating bone growth  
DATE-ISSUED: February 8, 2000

US-CL-CURRENT: 514/451; 514/460, 549/273

APPL-NO: 8/ 989862  
DATE FILED: December 12, 1997

**PARENT-CASE:**

This application claims priority under 35 USC 119 from provisional application Ser. No. 60/032,893 filed Dec. 31, 1996, the entire contents of which are incorporated herein by reference.

IN: Gasper; Shirley R., West; Robert R., Martinez; Theresa, Robbins; Kirk G., McKernan; Patricia A., Baidur; Nand, Labroo; Virender M.

AB: Compounds of the formula ##STR1## wherein X in each of formulas (1) and (2) represents a substituted or unsubstituted alkylene, alkenylene, or alkynylene linker of 2-6C;; Y represents one or more carbocyclic or heterocyclic rings; when two or more rings are present in Y, they may optionally be fused; and, R' represents a cation, H or a substituted or unsubstituted alkyl group of 1-6C; and, the dotted lines represent optional pi.-bonds,, promote bone formation and are thus useful in treating osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation.

L7: Entry 19 of 46

File: USPT

Feb 8, 2000

DOCUMENT-IDENTIFIER: US 6022887 A  
TITLE: Compositions and methods for stimulating bone growth

**ORPL:**

Rickard, D.J., et al., "Induction of Rapid Osteoblast Differentiation in Rat Bone Marrow Stromal Cell Cultures by Dexamethasone and BMP-2," Developmental Biology 161:218-228 (Jan. 1994).

20. Document ID: US 6008188 A

L7: Entry 20 of 46

File: USPT

Dec 28, 1999

US-PAT-NO: 6008188  
DOCUMENT-IDENTIFIER: US 6008188 A  
TITLE: Cytokine potentiator and pharmaceutical formulation for cytokine administration

DATE-ISSUED: December 28, 1999

US-CL-CURRENT: 514/2; 424/85.1, 424/85.2, 424/85.4, 514/561,  
514/667, 514/669, 514/673, 562/567,  
564/503

APPL-NO: 8/ 737064

DATE FILED: December 16, 1996

FOREIGN-APPL-PRIORITY-DATA:  
COUNTRY

	APPL-NO	APPL-DATE
JP	6-117495	May 6, 1994

PCT-DATA:

APPL-NO

DATE-FILED

PUB-NO

PUB-DATE

371-DATE

102(E)-DATE

PCT/JP95/00857

April 28, 1995

WO95/30412

Nov 16, 1995

Dec 16, 1996

Dec 16, 1996

IN: Oishi; Yuichi, Yoshida; Masaki, Inoue; Shintaro

AB: A cytokine activity enhancer comprising an ethanolamine derivative of the following general formula (I) or a salt thereof, or comprising it along with cytokine or a cytokine production promoter; and also a medicine for diseases with lowered cytokine activity, comprising, as the active ingredient, the cytokine activity enhancer:  
##STR1## wherein R.sub.1 is H, --CH.sub.2, --CH.sub.2 CH(CH.sub.3)OH or --CH.sub.2 CH.sub.2 OH; R.sub.2 is H, --CH.sub.3, --CH.sub.2 CH.sub.3 or --COOH; and R.sub.3 is H, --CH.sub.3, --CH.sub.2 CH.sub.3 or --CH.sub.2 NH.sub.2.

L7: Entry 20 of 46

File: USPT

Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6008188 A

TITLE: Cytokine potentiator and pharmaceutical formulation for cytokine administration

DEPR:

Cytokines as referred to herein include platelet-derived growth factor (hereinafter referred to as PDGF), fibroblast growth factor (hereinafter referred to as FGF), epidermal growth factor (hereinafter referred to as EGF), transforming growth factor (hereinafter referred to as TGF), bone morphogenetic protein (hereinafter referred to as BMP), interferon (hereinafter referred to as IFN), granulocyte colony-stimulating factor (hereinafter referred to as G-CSF), macrophage colony-stimulating factor (hereinafter referred to as M-CSF), insulin-like growth factor (hereinafter referred to as IGF), hepatocyte growth factor (hereinafter referred to as HGF), stem cell factor (hereinafter referred to as SCF), nerve growth factor (hereinafter referred to as NGF),

vascular endothelial cell growth factor (hereinafter referred to as VEGF), keratinocyte growth factor (hereinafter referred to as KGF), interleukin (see Interleukin Network, Kodan-sha, 1992, the entirety of which is herein incorporated by reference), and the like. Of these cytokines, those which activate tyrosine or serine/threonine kinases, and also activate the phosphorylation of tyrosine, or serine and/or threonine residues on subunits of tyrosine or serine/threonine kinase-linked receptors, respectively, are preferred effectors.

21. Document ID: US 5986056 A

L7: Entry 21 of 46

File: USPT

Nov 16, 1999

US-PAT-NO: 5986056

DOCUMENT-IDENTIFIER: US 5986056 A

TITLE: Chordin compositions

DATE-ISSUED: November 16, 1999

US-CL-CURRENT: 530/350; 435/69.1

APPL-NO: 9/ 130032

DATE FILED: August 4, 1998

PARENT-CASE:

This application is a divisional of U.S. Ser. No. 08/749,169, U.S. Pat. No. 5,846,770 filed Nov. 14, 1996, which application is a continuation-in-part of U.S. Ser. No. 08/343,760, filed Nov. 22, 1994, and now issued as U.S. Pat. No. 5,679,783.

IN: LaVallie; Edward R., Racie; Lisa A., DeRobertis; Edward M.

AB: Purified chordin proteins and processes for producing them are disclosed. DNA molecules encoding the chordin proteins are also disclosed. The proteins may be used in the treatment of bone, cartilage, other connective tissue defects and disorders, including tendon, ligament and meniscus, in wound healing and related tissue repair, as well for treatment of disorders and defects to tissue which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, brain, lung, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction inhibition of growth and/or differentiation of undifferentiated embryonic and stem cells. The proteins may be complexed with other proteins, particularly members of the transforming growth factor-beta superfamily of proteins.

L7: Entry 21 of 46

File: USPT

Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5986056 A

TITLE: Chordin compositions

BSPR:

The chordin proteins of the present invention, include polypeptides having a molecular weight of

about 105-110 kd, said polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and having the ability to bind to TGF-.beta. and/or BMP proteins, or the ability to alter or influence the formation of cartilage and/or bone and/or other connective tissues, such as exhibited in the embryonic stem cell and Rosen-Modified Sampath-Reddi ectopic implant assays, described in the examples.

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

22. Document ID: US 5976523 A

L7: Entry 22 of 46

File: USPT

Nov 2, 1999

US-PAT-NO: 5976523

DOCUMENT-IDENTIFIER: US 5976523 A

TITLE: Method for healing compromised tissues using pyrimidine derivatives

DATE-ISSUED: November 2, 1999

US-CL-CURRENT: 424/85.1; 514/228.5, 514/234.2, 514/252.16, 514/258, 530/300, 530/350

APPL-NO: 8/ 656158

DATE FILED: May 16, 1996

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY

APPL-NO

APPL-DATE

JP

7-141074

May 16, 1995

JP

8-071329

March 2, 1996

IN: Awaya; Akira, Ito; Fumiaki, Torigoe; Kojun, Tomino; Ikuo

AB: The present invention provides a method for the screening of a wound-healing agent, which comprises determining a substance to be active as a wound-healing

agent on the basis of potentiation or modification of biological activities of a growth and/or differentiation factor, a growth hormone or a cytokine. This invention also provides a wound-healing method, which comprises as an active ingredient a compound of the following formula (1) or formula (2) found to be active by the screening method. ##STR1##

L7: Entry 22 of 46

File: USPT

Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5976523 A

TITLE: Method for healing compromised tissues using pyrimidine derivatives

CLPR:

7. A method according to claim 3, wherein said biological activities are activities of at least one biological substance selected from the group consisting of an epidermal growth factor (EGF), an acidic fibroblast growth factor (aFGF), a basic fibroblast growth factor (bFGF), an .alpha. or .beta. transforming growth factor (TGF), a vascular endothelial cell growth factor (VEGF), a platelet-derived growth factor (PDGF), a platelet-derived endothelial cell growth factor (PDECGF), a bone morphogenic protein (BMP), a hepatocyte growth factor (HGF), midkine, a tumor necrosis factor (TNF), insulin, an insulin-like growth factor (IGF-I, II), a keratinocyte growth factor, an endothelial cell growth factor (ECGF), a fibroblast-derived epithelial cell growth factor, a granulocyte-colony stimulating factor (G-CSF), a macrophage-colony stimulating factor (M-CSF), a granulocyte-macrophage-colonystimulating factor (GM-CSF), thrombopoietin (TPO), a leukemia inhibitory factor (LIF), a stem cell factor (SCF), erythropoietin (EPO), an adult T cell leukemia-derived factor (ADF), macrophage inflammatory protein 1.alpha.(MIP-1.alpha.), transferrin, thrombin, thrombomodulin, interleukin-1 (IL-1), interleukin- (IL4), interleukin-6 (IL-6), interleukin-8 (IL-8), a heparin releasing factor (HRF), a monocyte chemotactic activator, a calcitonin gene related peptide (CGRP), superoxide dismutase (SOD), an angiotensin, a prostaglandin, serotonin, collagen, fibronectin, laminin and a homologue of any of the foregoing..

23. Document ID: US 5972368 A

L7: Entry 23 of 46

File: USPT

Oct 26, 1999

US-PAT-NO: 5972368

DOCUMENT-IDENTIFIER: US 5972368 A

TITLE: Bone graft composites and spacers

DATE-ISSUED: October 26, 1999

US-CL-CURRENT: 424/423; 424/422, 424/426, 514/2, 530/840

APPL-NO: 8/ 873276

DATE FILED: June 11, 1997

IN: McKay; William F.

AB: A bone graft substitute including a composition of natural selectively deactivated bone material which has been processed to remove associated non-collagenous bone proteins, said bone material containing native collagen materials and naturally associated bone minerals and substantially free from native non-collagenous protein, and a therapeutically effective amount to stimulate bone growth of a bone growth factor in a pharmaceutically acceptable carrier in synergistic combination with said bone material. Spacers composed of the bone graft substitute composition methods for using the spacers are also provided.

L7: Entry 23 of 46

File: USPT

Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972368 A  
TITLE: Bone graft composites and spacers

DRPR:

This invention provides the further advantage of exploiting the discovery that bone mineral is an excellent carrier for osteogenic factors such as bone morphogenic proteins. Hydroxyapatite which is very similar in chemical composition to the mineral in cortical bone is an osteogenic factor-binding agent which controls the rate of delivery of certain proteins to the fusion site. Calcium phosphate compositions such as hydroxyapatite are thought to bind bone morphogenic proteins and prevent BMP from prematurely dissipating from the spacer before fusion can occur. It is further believed that retention of the BMP by the agent permits the protein to initiate the transformation of mesenchymal stem cells into bone producing cells or osteoblasts within the device at a rate that is conducive to complete and rapid bone formation and ultimately, fusion across the disc space. The spacers of this invention have the advantage of including a load bearing member composed of selectively deactivated bone which naturally binds and provides controlled delivery of osteogenic factors such as bone morphogenic proteins.

24. Document ID: US 5965403 A

L7: Entry 24 of 46

File: USPT

Oct 12, 1999

US-PAT-NO: 5965403  
DOCUMENT-IDENTIFIER: US 5965403 A  
TITLE: Nucleic acids encoding bone morphogenic protein-16 (BMP-16)  
DATE-ISSUED: October 12, 1999

US-CL-CURRENT: 435/69.4; 435/252.3, 435/320.1, 435/325, 435/69.1, 435/69.7, 536/23.1, 536/23.5, 536/23.51, 536/24.1

APPL-NO: 8/ 715202  
DATE FILED: September 18, 1996

IN: Celeste; Anthony J., Murray; Beth L.

AB: Purified BMP-16 proteins and processes for producing them are disclosed. DNA molecules encoding the BMP-16 proteins are also disclosed. The proteins may be used in the treatment of bone, cartilage, other connective tissue defects and disorders, including tendon, ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, lung, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells.

L7: Entry 24 of 46

File: USPT

Oct 12, 1999

DOCUMENT-IDENTIFIER: US 5965403 A  
TITLE: Nucleic acids encoding bone morphogenic protein-16 (BMP-16)

BSPR:

The BMP-16 DNA sequence (SEQ ID NO: 1) and amino acid sequence (SEQ ID NO: 2) are set forth in the Sequence Listings. BMP-16 proteins may be capable of inducing the formation of cartilage, bone, or other connective tissue, or combinations thereof. The cartilage and/or bone and/or other connective tissue formation activity in the rat bone formation assay described below. BMP-16 proteins may be further characterized by the ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may also be useful for treating cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation of the cells.

BSPR:

It is expected that other species, particularly human, have DNA sequences homologous to human BMP-16 protein. The invention, therefore, includes methods for obtaining the DNA sequences encoding human BMP-16 protein, the DNA sequences obtained by those methods, and the human protein encoded by those DNA sequences. This method entails utilizing the human BMP-16 protein nucleotide sequence or portions thereof to design probes to screen libraries for the corresponding gene from other species or coding sequences or fragments thereof from using standard techniques. Thus, the present invention may include DNA sequences from other species, which are homologous to human BMP-16 protein and can be obtained using the human BMP-16 sequence. The present invention may also include functional fragments of the human BMP-16 protein, and DNA sequences encoding such functional fragments, as well as functional fragments of other related proteins. The ability of such a fragment to function is determinable by assay of the protein in the biological assays described for the assay of the BMP-16 protein. A DNA sequence encoding the complete mature human BMP-16 protein (SEQ ID NO:1) and the corresponding amino acid sequence (SEQ ID NO:2) are set forth herein. The BMP-16 proteins of the present invention, such as human BMP-16, may be produced by culturing a cell transformed with the correlating DNA sequence, such as the human BMP-16 DNA sequence, and recovering and purifying protein, such as BMP-16, from the culture medium. The purified expressed protein is substantially free from other proteinaceous materials with which it is co-produced, as well as from other

contaminants. The recovered purified protein is contemplated to exhibit cartilage and/or bone and/or connective tissue formation activity. Thus, the proteins of the invention may be further characterized by the ability to demonstrate cartilage and/or bone and/or other connective tissue formation activity in the rat bone formation assay described below. BMP-16 proteins may be further characterized by the ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may also be characterized by their ability to enhance or enrich the growth and/or differentiation of the cells.

**BSPR:**

The purified proteins of the present inventions may be used to generate antibodies, either monoclonal or polyclonal, to human BMP-16 and/or other BMP-16-related proteins, using methods that are known in the art of antibody production. Thus, the present invention also includes antibodies to human BMP-16 and/or other related proteins. The antibodies may be useful for purification of BMP-16 and/or other BMP-16 related proteins, or for inhibiting or preventing the effects of BMP-16 related proteins. The BMP-16 protein and related proteins may be useful for inducing the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may also be useful for treating relatively undifferentiated cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation of the cells. The treated cell populations may be useful for implantation and for gene therapy applications.

**BSPR:**

The BMP-16 proteins recovered from the culture medium are purified by isolating them from other proteinaceous materials from which they are co-produced and from other contaminants present. BMP-16 proteins may be characterized by the ability to induce the formation of cartilage and/or bone and/or other connective tissue and other tissue repair and differentiation, for example, in the rat bone formation assay described below. In addition, BMP-16 proteins may be further characterized by their effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may be characterized by the embryonic stem cell assay described below.

**DEPR:**

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by

BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

**DEPR:**

In order to assay the effects of the BMP-16 proteins of the present invention, it is possible to assay the growth and differentiation effects in vitro on a number of available embryonic stem cell lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection 10801 University Boulevard, Manassas, Va. 20110-2209.

25. Document ID: US 5942225 A

L7: Entry 25 of 46

File: USPT

Aug 24, 1999

US-PAT-NO: 5942225

DOCUMENT-IDENTIFIER: US 5942225 A

TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation

DATE-ISSUED: August 24, 1999

US-CL-CURRENT: 424/93.7; 435/366, 435/372

APPL-NO: 8/ 899414

DATE FILED: July 23, 1997

**PARENT-CASE:**

This application is a divisional of U.S. application Ser. No. 08/377,461 filed Jan. 24, 1995, now U.S. Pat. No. 5,736,396.

IN: Bruder; Scott P., Caplan; Arnold I., Haynesworth; Stephen E.

**AB:** Methods for in vitro or ex vivo lineage directed induction of isolated, culture expanded human mesenchymal stem cells comprising contacting the mesenchymal stem cells with a bioactive factor effective to induce differentiation thereof into a lineage of choice as well as such compositions including isolated culture expanded human mesenchymal stem cells and bioactive factors effective to induce directed lineage induction are disclosed. Further disclosed is this method which also includes introducing such culturally expanded lineage-induced mesenchymal stem cells into a host from which they have originated for purposes of mesenchymal tissue regeneration or repair.

L7: Entry 25 of 46

File: USPT

Aug 24, 1999

DOCUMENT-IDENTIFIER: US 5942225 A

TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation

**DEPR:**

Factors which stimulate osteogenesis (i.e. are osteoinductive) from isolated human mesenchymal stem cells in accordance with the invention are present in several classes of molecules, including the following: bone morphogenic proteins, such as BMP-2 (14) and BMP-3 (15); growth factors, such as



basic fibroblast growth factor (bFGF); glucocorticoids, such as dexamethasone (16); and prostaglandins, such as prostaglandin E1 (22). Further, ascorbic acid and its analogs, such as ascorbic acid-2-phosphate (17) and glycerol phosphates, such as .beta.-glycerophosphate (18) are effective adjunct factors for advanced differentiation, although alone they do not induce osteogenic differentiation.

26. Document ID: US 5939388 A

L7: Entry 26 of 46

File: USPT

Aug 17, 1999

US-PAT-NO: 5939388  
DOCUMENT-IDENTIFIER: US 5939388 A  
TITLE: Methods of administering BMP-5 compositions  
DATE-ISSUED: August 17, 1999

US-CL-CURRENT: 514/12; 424/85.1, 514/2

APPL-NO: 8/ 788729  
DATE FILED: January 23, 1997

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No.

08/469,935, filed Jun. 6, 1995, now U.S. Pat. No. 5,635,373, which is a divisional of U.S. Ser. No.

08/116,425, filed Sep. 7, 1993, now U.S. Pat. No. 5,543,394, which is a continuation of U.S. Ser.

No. 07/995,565, filed Dec. 22, 1992, now abandoned, which is a continuation of U.S. Ser.

No.07/588,227, filed Sep. 26, 1990, now abandoned, which is a continuation-in-part of U.S. Ser. No.

07/437,409, filed Nov. 15, 1989, now abandoned; which is a continuation-in-part of U.S. Ser. No.

07/370,547, filed Jun. 23, 1989, now U.S. Pat. No. 5,106,748; which is a continuation-in-part of

U.S. Ser. No. 07/347,559, filed May 4, 1989, now abandoned; which is a continuation-in-part of U.S.

Ser. No. 07/329,610, filed Mar. 28, 1989, now abandoned, which is a continuation-in-part of U.S.

Ser. No. 07/179,100, now U.S. Pat. No. 5,013,649, U.S. Ser. No. 07/179,101, now abandoned, and U.S.

Ser. No. 07/179,197, now abandoned; each filed Apr. 8, 1988, which are continuations-in-part of U.S.

Ser. No. 07/028,285, filed Mar. 20, 1987, now abandoned, and U.S. Ser. No. 07/031,346, filed Mar.

26, 1987, now U.S. Pat. No. 4,877,864, which are continuations-in-part of U.S. Ser. No. 06/943,332, filed Dec. 17, 1986, now abandoned, and Ser. No. 06/880,776, filed Jul. 1, 1986, now abandoned.

IN: Rosen; Vicki A., Wozney; John M., Wang; Elizabeth A.

AB: Purified BMP-5 proteins and processes for producing them are disclosed. The proteins may be used in the treatment of bone and/or cartilage defects and in wound healing and related tissue repair.

L7: Entry 26 of 46

File: USPT

Aug 17, 1999

DOCUMENT-IDENTIFIER: US 5939388 A  
TITLE: Methods of administering BMP-5 compositions

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

DEPR:

In order to assay the effects of the BMP-5 proteins of the present invention, it is possible to assay the growth and differentiation effects in vitro on a number of available embryonic stem cell lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection in Rockville, Md.

27. Document ID: US 5939323 A

L7: Entry 27 of 46

File: USPT

Aug 17, 1999

US-PAT-NO: 5939323  
DOCUMENT-IDENTIFIER: US 5939323 A  
TITLE: Hyaluronan based biodegradable scaffolds for tissue repair  
DATE-ISSUED: August 17, 1999

US-CL-CURRENT: 435/395; 424/426

APPL-NO: 8/ 864709  
DATE FILED: May 28, 1997

PARENT-CASE:

RELATED APPLICATIONS This application claims priority under 35 USC .sectn. 119(e) from U.S. provisional patent application Ser. No. 60/018,492 filed on May 28, 1996, entitled Hyaluronan Based Biodegradable Scaffolds for Tissue Repair. The contents of the provisional application are hereby expressly incorporated by reference.

IN: Valentini; Robert F., Kim; Hyun D.

AB: A hyaluronic acid derivitized scaffold and method of forming are disclosed. The scaffolds are useful for various medical purposes such as tissue repair, tissue reconstruction and wound healing. In order to enhance these processes the scaffolds may

be engineered to  
incorporate biologically active molecules such as BMP.

L7: Entry 27 of 46

File: USPT

Aug 17, 1999

DOCUMENT-IDENTIFIER: US 5939323 A  
TITLE: Hyaluronan based biodegradable scaffolds for tissue repair

DEPR:

3. BMP Release Bioassay by Alkaline Phosphatase (AP) Induction of  
Pluripotent Stem Cells

from adult mice by  
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston,  
Mass. Treatment of W-20  
cells with certain BMP proteins results in (1) increased alkaline  
phosphatase production, (2)  
induction of PTH stimulated cAMP, and (3) induction of osteocalcin  
synthesis by the cells. While (1)  
and (2) represent characteristics associated with the osteoblast phenotype,  
the ability to  
synthesize osteocalcin is a phenotypic property only displayed by mature  
osteoblasts. Furthermore,  
to date we have observed conversion of W-20 stromal cells to  
osteoblast-like cells only upon  
treatment with BMPs. In this manner, the in vitro activities displayed by  
BMP treated W-20 cells  
correlate with the in vivo bone forming activity known for BMPs.

28. Document ID: US 5932216 A

L7: Entry 28 of 46

File: USPT

Aug 3, 1999

US-PAT-NO: 5932216  
DOCUMENT-IDENTIFIER: US 5932216 A  
TITLE: Antibodies to bone morphogenetic protein-10 (BMP-10)  
DATE-ISSUED: August 3, 1999

US-CL-CURRENT: 424/158.1; 424/139.1

APPL-NO: 8/ 926885  
DATE FILED: September 10, 1997

PARENT-CASE:

This application is a continuation of application Ser. No. 453,942, filed  
May 30, 1995, U.S. Pat.  
No. 5,703,043, which is a divisional of Ser. No. 08/247,908 filed May 20,  
1994 (issued Jun. 10, 1994  
as U.S. Pat. No. 5,637,480); which is a continuation-in-part of Ser. No.  
08/061,695 filed May 12,  
1993 (abandoned).

IN: Celeste; Anthony J., Wozney; John M.

AB: Purified Bone Morphogenetic Protein-10(BMP-10) proteins and  
processes for producing  
them are disclosed. DNA molecules encoding the BMP-10 proteins are  
also disclosed. The proteins  
may be used in the treatment of bone and cartilage defects and in wound  
healing and related  
tissue repair.

L7: Entry 28 of 46

File: USPT

Aug 3, 1999

DOCUMENT-IDENTIFIER: US 5932216 A  
TITLE: Antibodies to bone morphogenetic protein-10 (BMP-10)

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is  
based upon the conversion of  
these cells to osteoblast-like cells after treatment with a BMP protein  
[Thies et al, Journal of  
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology,  
130:1318 (1992)].  
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived

29. Document ID: US 5866364 A

L7: Entry 29 of 46

File: USPT

Feb 2, 1999

US-PAT-NO: 5866364  
DOCUMENT-IDENTIFIER: US 5866364 A  
TITLE: Recombinant bone morphogenetic protein heterodimers  
DATE-ISSUED: February 2, 1999

US-CL-CURRENT: 435/69.1; 435/252.3, 435/252.33, 435/255.1,  
435/320.1, 435/325, 435/70.2, 530/350,  
530/399, 536/23.5

APPL-NO: 7/ 989847  
DATE FILED: November 27, 1992

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS This application  
is a continuation-in-part of U.S. Ser. No.  
07/864,692 filed Apr. 7, 1992, now abandoned which is a  
continuation-in-part of U.S. Ser. No.  
07/787,496 filed Nov. 4, 1991 now abandoned.

FOREIGN-APPL-PRIORITY-DATA:  
COUNTRY

APPL-NO

APPL-DATE

WO

PCT/US92/09430

November 2, 1992

IN: Israel; David, Wolfman; Neil M.

AB: The present invention relates to a methods for producing  
recombinant heterodimeric  
BMP proteins useful in the field of treating bone defects, healing bone  
injury and in wound  
healing in general. The invention also relates to the recombinant  
heterodimers and compositions  
containing them.

L7: Entry 29 of 46

File: USPT

Feb 2, 1999

DOCUMENT-IDENTIFIER: US 5866364 A  
TITLE: Recombinant bone morphogenetic protein heterodimers

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al, "Bone Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and Mineral Research, 5(2):305 (1990); and R. S. Thies et al, "Recombinant Human Bone Morphogenetic Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology, in press (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. BMP-2 treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

30. Document ID: US 5846770 A

L7: Entry 30 of 46

File: USPT

Dec 8, 1998

US-PAT-NO: 5846770

DOCUMENT-IDENTIFIER: US 5846770 A

TITLE: DNA molecules encoding human chordin

DATE-ISSUED: December 8, 1998

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 435/69.7, 536/23.4, 536/23.5

APPL-NO: 8/ 749169

DATE FILED: November 14, 1996

PARENT-CASE:

This application is a continuation-in-part from Ser. No. 343,760, filed on Nov. 22, 1994, and issued as U.S. Pat. No. 5,679,783.

IN: LaVallie; Edward R., Racie; Lisa A., DeRobertis; Edward M.

AB: Purified chordin proteins and processes for producing them are disclosed. DNA molecules encoding the chordin proteins are also disclosed. The proteins may be used in the treatment of bone, cartilage, other connective tissue defects and disorders, including tendon, ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, brain, lung, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction and/or differentiation of undifferentiated embryonic and stem cells. The proteins may be complexed with other proteins, particularly members of the transforming

growth factor-beta superfamily of proteins.

L7: Entry 30 of 46

File: USPT

Dec 8, 1998

DOCUMENT-IDENTIFIER: US 5846770 A

TITLE: DNA molecules encoding human chordin

BSPR:

The chordin proteins of the present invention, include polypeptides having a molecular weight of about 105-110 kd, said polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and having the ability to bind to TGF-.beta. and/or BMP proteins, or the ability to alter or influence the formation of cartilage and/or bone and/or other connective tissues, such as exhibited in the embryonic stem cell and Rosen-Modified Sampath-Reddi ectopic implant assays, described in the examples.

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5: 305 (1990); and Thies et al, Endocrinology, 130: 1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

31. Document ID: US 5804416 A

L7: Entry 31 of 46

File: USPT

Sep 8, 1998

US-PAT-NO: 5804416

DOCUMENT-IDENTIFIER: US 5804416 A

TITLE: Mutants of bone morphogenetic proteins

DATE-ISSUED: September 8, 1998

US-CL-CURRENT: 435/69.1; 530/333, 530/350, 530/399

APPL-NO: 8/ 741589

DATE FILED: October 31, 1996

PARENT-CASE:

This application is a divisional of application Ser. No. 08/360,914, filed Dec. 21, 1994, which has issued as U.S. Pat. No. 5,756,308 which application is a

continuation-in-part of PCT application  
PCT/US94/13181, filed on Nov. 15, 1994, which is a continuation-in-part  
of application Ser. No.  
08/163,877, filed on Dec. 7, 1993, which has issued as U.S. Pat. No.  
5,399,677.

IN: Wolfman; Neil M., McCoy; John

AB: DNA molecules encoding mutant forms of bone morphogenetic  
proteins (BMP) are  
disclosed. The mutant forms of BMP can be produced bacterially and  
refolded to produce  
biologically active homodimers or heterodimers of BMP. A method of  
making such mutant BMPs is  
also disclosed.

L7: Entry 31 of 46

File: USPT

Sep 8, 1998

DOCUMENT-IDENTIFIER: US 5804416 A  
TITLE: Mutants of bone morphogenetic proteins

DEPR:

The in vitro biological activity of the refolded bone morphogenetic proteins  
is monitored by the

W-20 assay as set forth in Example 9. Use of the W-20-17 bone marrow  
stromal cells as an indicator  
cell line is based upon the conversion of these cells to osteoblast-like cells  
after treatment with

BMP [R. S. Thies et al., Journal of Bone and Mineral Research 5(2):305  
(1990); and R. S. Thies et

al., Endocrinology 130:1318-1324 (1992)]. W-20-17 cells are a clonal  
bone marrow stromal cell line  
derived from adult mice by researchers in the laboratory of Dr. D. Nathan,  
Children's Hospital,

Boston, Mass. Treatment of W-20-17 cells with BMP results in (1)  
increased alkaline phosphatase  
production, (2) induction of parathyroid hormone stimulated cAMP, and  
(3) induction of osteocalcin  
synthesis by the cells. While (1) and (2) represent characteristics  
associated with the osteoblast

phenotype, the ability to synthesize osteocalcin is a phenotypic property  
only displayed by mature  
osteoblasts. Furthermore, to date the conversion of W-20-17 stromal cells  
to osteoblast-like cells

has been observed only upon treatment with bone morphogenetic proteins.  
The in vivo biological

activity of the refolded bone morphogenetic proteins is monitored by a  
modified version of the rat

bone formation assay described in Sampath and Reddi, Proc. Natl. Acad.  
Sci. USA, 80:6591-6595 (1983)

herein called the Rosen-modified Sampath-Reddi assay, as set forth in  
Example 10.

32. Document ID: US 5756457 A

L7: Entry 32 of 46

File: USPT

May 26, 1998

US-PAT-NO: 5756457  
DOCUMENT-IDENTIFIER: US 5756457 A  
TITLE: Neural regeneration using human bone morphogenetic proteins  
DATE-ISSUED: May 26, 1998

US-CL-CURRENT: 514/12; 424/422, 424/423, 606/152

APPL-NO: 8/ 435120  
DATE FILED: May 5, 1995

PARENT-CASE:

RELATED APPLICATIONS The present application is a  
continuation-in-part of Ser. No. 08/112,492, filed  
on Aug. 26, 1993, which has been abandoned.

IN: Wang; Elizabeth A., D'Alessandro; Josephine S., Toriumi; Dean  
M.

AB: Methods and devices are disclosed for inducing growth of neural  
cells, and repairing  
neural defects in a mammal. The method comprises administering to said  
mammal at the site of  
neural defect, damage or depletion, an effective amount of a bone  
morphogenetic protein, either  
in admixture with a pharmaceutically acceptable vehicle, or adsorbed to a  
suitable matrix. The  
device comprises bone morphogenetic protein, optionally in combination  
with other factors,  
adsorbed on a suitable matrix and contained within an artificial nerve  
replacement vessel.

L7: Entry 32 of 46

File: USPT

May 26, 1998

DOCUMENT-IDENTIFIER: US 5756457 A  
TITLE: Neural regeneration using human bone morphogenetic proteins

BSPR:

In accordance with the method of the invention, BMP, such as rhBMP-2,  
may be administered alone, in  
combination with other BMPs, or in combination with other therapies. For  
example, rhBMP-2 may be  
efficaciously combined with a cytokine, lymphokine, growth factor, or  
colony stimulating factor, in  
the treatment of neural diseases. Exemplary cytokines, lymphokines,  
growth factors, and colony  
stimulating factors for use in combination with BMP in accordance with  
the method of the invention  
include, without limitation, EGF, FGF, interleukins 1 through 12, M-CSF,  
G-CSF, GM-CSF, stem cell  
factor, erythropoietin, and the like. In addition, the BMPs may be  
combined with neurotrophic  
factors such as CNTF, LIF, IL-6 and insulin-like growth factors [IGFs].  
Additionally, proteins  
normally found in the neural environment may be added to the BMPs in  
accordance with the present  
invention. These may include laminin, hyalauronic acid and chondroitin  
sulfate proteoglycans,  
including versican.

33. Document ID: US 5756308 A

L7: Entry 33 of 46

File: USPT

May 26, 1998

US-PAT-NO: 5756308  
DOCUMENT-IDENTIFIER: US 5756308 A  
TITLE: Refolding variant of bone morphogenetic protein-8  
DATE-ISSUED: May 26, 1998

US-CL-CURRENT: 435/69.1; 530/333, 530/399, 536/23.5

APPL-NO: 8/ 360914  
DATE FILED: December 21, 1994

PARENT-CASE:

The present application is a continuation-in-part of Ser. No. 08/163,877, filed on Dec. 7, 1993, which has issued as U.S. Pat. No. 5,399,677, and claims priority from PCT application Ser. No. PCT/US94/13181, filed on Nov. 15, 1994.

IN: Wolfman; Neil M., McCoy; John

AB: DNA molecules encoding mutant forms of bone morphogenetic proteins (BMP) are disclosed. The mutant forms of BMP can be produced bacterially and refolded to produce biologically active homodimers or heterodimers of BMP. A method of making such mutant BMPs is also disclosed.

L7: Entry 33 of 46

File: USPT

May 26, 1998

DOCUMENT-IDENTIFIER: US 5756308 A  
TITLE: Refolding variant of bone morphogenetic protein-8

DEPR:

The in vitro biological activity of the refolded bone morphogenetic proteins is monitored by the

W-20 assay as set forth in Example 9. Use of the W-20-17 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with

BMP [R. S. Thies et al., Journal of Bone and Mineral Research 5(2):305 (1990); and R. S. Thies et al., Endocrinology 130:1318-1324 (1992)]. W-20-17 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital,

Boston, MA. Treatment of W-20-17 cells with BMP results in (1) increased alkaline phosphatase production, (2) induction of parathyroid hormone stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date the conversion of W-20-17 stromal cells to osteoblast-like cells

has been observed only upon treatment with bone morphogenetic proteins. The in vivo biological

activity of the refolded bone morphogenetic proteins is monitored by a modified version of the rat

bone formation assay described in Sampath and Reddi, Proc. Natl. Acad. Sci. USA, 80:6591-6595 (1983)

herein called the Rosen-modified Sampath-Reddi assay, as set forth in Example 10.

34. Document ID: US 5736396 A

L7: Entry 34 of 46

File: USPT

Apr 7, 1998

US-PAT-NO: 5736396  
DOCUMENT-IDENTIFIER: US 5736396 A

TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation

DATE-ISSUED: April 7, 1998

US-CL-CURRENT: 435/366; 424/93.7, 435/372

APPL-NO: 8/ 377461  
DATE FILED: January 24, 1995

IN: Bruder; Scott P., Caplan; Arnold I., Haynesworth; Stephen E.

AB: Methods for in vitro or ex vivo lineage directed induction of isolated, culture expanded human mesenchymal stem cells comprising contacting the mesenchymal stem cells with a bioactive factor effective to induce differentiation thereof into a lineage of choice as well as such compositions including isolated culture expanded human mesenchymal stem cells and bioactive factors effective to induce directed lineage induction are disclosed. Further disclosed is this method which also includes introducing such culturally expanded lineage-induced mesenchymal stem cells into a host from which they have originated for purposes of mesenchymal tissue regeneration or repair.

L7: Entry 34 of 46

File: USPT

Apr 7, 1998

DOCUMENT-IDENTIFIER: US 5736396 A  
TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation

DEPR:

Factors which stimulate osteogenesis (i.e. are osteoinductive) from isolated human mesenchymal stem

cells in accordance with the invention are present in several classes of molecules, including the

following: bone morphogenic proteins, such as BMP-2 (14) and BMP-3 (15); growth factors, such as

basic fibroblast growth factor (bFGF); glucocorticoids, such as dexamethasone (16); and prostaglandins, such as prostaglandin E1 (22). Further, ascorbic acid and its analogs, such as ascorbic acid-2-phosphate (17) and glycerol phosphates, such as .beta.-glycerophosphate (18) are effective adjunct factors for advanced differentiation, although alone they do not induce osteogenic differentiation.

35. Document ID: US 5728679 A

L7: Entry 35 of 46

File: USPT

Mar 17, 1998

US-PAT-NO: 5728679  
DOCUMENT-IDENTIFIER: US 5728679 A  
TITLE: BMP-15 compositions  
DATE-ISSUED: March 17, 1998

US-CL-CURRENT: 514/12; 424/484, 530/350, 530/387.1, 530/395, 530/399

APPL-NO: 8/ 798665

DATE FILED: February 11, 1997

PARENT-CASE:

This application is a division of application Ser. No. 08/446,924, filed May 18, 1995 now U.S. Pat. No. 5,635,372.

IN: Celeste; Anthony J., Dube; Jennifer L., Lyons; Karen M., Hogan; Brigid

AB: Purified BMP-15-related proteins and processes for producing them are disclosed. DNA molecules encoding the BMP-15-related proteins are also disclosed. The proteins may be used in the treatment of bone and cartilage and/or other connective tissue defects and in wound healing and related tissue repair.

L7: Entry 35 of 46

File: USPT

Mar 17, 1998

DOCUMENT-IDENTIFIER: US 5728679 A  
TITLE: BMP-15 compositions

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

36. Document ID: US 5703043 A

L7: Entry 36 of 46

File: USPT

Dec 30, 1997

US-PAT-NO: 5703043  
DOCUMENT-IDENTIFIER: US 5703043 A  
TITLE: Bone morphogenetic protein-10 (BMP-10) compositions  
DATE-ISSUED: December 30, 1997

US-CL-CURRENT: 514/12; 435/69.1, 530/399, 536/23.5, 930/120

APPL-NO: 8/453942  
DATE FILED: May 30, 1995

PARENT-CASE:

This application is a Divisional of U.S. Ser. No. 08/247,908, filed as PCT/US94/05290 May 12, 1994, U.S. Pat. No. 5,637,430, which is a Continuation-in-part of U.S. Ser. No. 08/061,695 filed May 12, 1993 (abandoned).

IN: Celeste; Anthony J., Wozney; John M.

AB: Purified Bone Morphogenetic Protein-10 (BMP-10) proteins and processes for producing them are disclosed. DNA molecules encoding the BMP-10 proteins are also disclosed. The proteins may be used in the treatment of bone and cartilage defects and in wound healing and related tissue repair.

L7: Entry 36 of 46

File: USPT

Dec 30, 1997

DOCUMENT-IDENTIFIER: US 5703043 A  
TITLE: Bone morphogenetic protein-10 (BMP-10) compositions

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

37. Document ID: US 5700911 A

L7: Entry 37 of 46

File: USPT

Dec 23, 1997

US-PAT-NO: 5700911  
DOCUMENT-IDENTIFIER: US 5700911 A  
TITLE: Bone morphogenetic protein -11 (BMP-11) compositions  
DATE-ISSUED: December 23, 1997

US-CL-CURRENT: 530/350; 435/69.4, 530/399, 930/120

APPL-NO: 8/452772  
DATE FILED: May 30, 1995

PARENT-CASE:

This application is a Divisional of U.S. Ser. No. 08/247,907 filed May 20, 1994 now U.S. Pat. No.

5,639,638, which is a continuation-in-part of U.S. Ser. No. 08/061,464  
filed May 12, 1993  
(abandoned).

IN: Wozney; John M., Celeste; Anthony J.

AB: Purified Bone Morphogenetic Protein-11(BMP-11) proteins and  
processes for producing  
them are disclosed. Recombinant DNA molecules encoding the BMP-11  
proteins are also disclosed.

The proteins may be useful in regulating follicle stimulating hormone,  
such as for  
contraception. In addition, the proteins may be useful for the induction of  
bone, cartilage  
and/or other connective tissue.

L7: Entry 37 of 46

File: USPT

Dec 23, 1997

DOCUMENT-IDENTIFIER: US 5700911 A

TITLE: Bone morphogenetic protein -11 (BMP-11) compositions

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is  
based upon the conversion of  
these cells to osteoblast-like cells after treatment with a BMP protein  
[Thies et al, Journal of  
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology,  
130:1318 (1992)].  
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived  
from adult mice by  
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston,  
Mass. Treatment of W-20  
cells with certain BMP proteins results in (1) increased alkaline  
phosphatase production, (2)  
induction of PTH stimulated cAMP, and (3) induction of osteocalcin  
synthesis by the cells. While (1)  
and (2) represent characteristics associated with the osteoblast phenotype,  
the ability to  
synthesize osteocalcin is a phenotypic property only displayed by mature  
osteoblasts. Furthermore,  
to date we have observed conversion of W-20 stromal cells to  
osteoblast-like cells only upon  
treatment with BMPs. In this manner, the in vitro activities displayed by  
BMP treated W-20 cells  
correlate with the in vivo bone forming activity known for BMPs.

38. Document ID: US 5639638 A

L7: Entry 38 of 46

File: USPT

Jun 17, 1997

US-PAT-NO: 5639638

DOCUMENT-IDENTIFIER: US 5639638 A

TITLE: DNA molecules encoding bone morphogenetic protein-11

DATE-ISSUED: June 17, 1997

US-CL-CURRENT: 435/69.4; 435/252.3, 435/320.1, 435/325, 435/358,  
435/360, 435/364, 530/399,  
536/23.4, 536/23.51, 930/120

APPL-NO: 8/ 247907

DATE FILED: May 20, 1994

PARENT-CASE:

BACKGROUND OF THE INVENTION This application is a  
Continuation-in-part application of Ser. No.  
08/061,464 filed on May 12, 1993 presently abandoned.

IN: Wozney; John M., Celeste; Anthony J.

AB: Purified Bone Morphogenetic Protein-11 proteins and processes  
for producing them are  
disclosed. Recombinant DNA molecules encoding the BMP-11 proteins  
are also disclosed. The  
proteins may be useful in regulating follicle stimulating hormone, such as  
for contraception,  
and for the induction of bone, cartilage and/or other connective tissue.

L7: Entry 38 of 46

File: USPT

Jun 17, 1997

DOCUMENT-IDENTIFIER: US 5639638 A

TITLE: DNA molecules encoding bone morphogenetic protein-11

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is  
based upon the conversion of  
these cells to osteoblast-like cells after treatment with a BMP protein  
[Thies et al, Journal of  
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology,  
130:1318 (1992)].  
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived  
from adult mice by  
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston,  
Mass. Treatment of W-20  
cells with certain BMP proteins results in (1) increased alkaline  
phosphatase production, (2)  
induction of PTH stimulated cAMP, and (3) induction of osteocalcin  
synthesis by the cells. While (1)  
and (2) represent characteristics associated with the osteoblast phenotype,  
the ability to  
synthesize osteocalcin is a phenotypic property only displayed by mature  
osteoblasts. Furthermore,  
to date we have observed conversion of W-20 stromal cells to  
osteoblast-like cells only upon  
treatment with BMPs. In this manner, the in vitro activities displayed by  
BMP treated W-20 cells  
correlate with the in vivo bone forming activity known for BMPs. Below  
two in vitro assays useful in  
comparison of BMP activities of novel osteoinductive molecules are  
described.

39. Document ID: US 5637480 A

L7: Entry 39 of 46

File: USPT

Jun 10, 1997

US-PAT-NO: 5637480

DOCUMENT-IDENTIFIER: US 5637480 A

TITLE: DNA molecules encoding bone morphogenetic protein-10

DATE-ISSUED: June 10, 1997

US-CL-CURRENT: 435/69.4; 435/252.3, 435/320.1, 435/325, 435/360,  
435/364, 435/365.1, 530/399,  
536/23.4, 536/23.51, 930/10

APPL-NO: 8/ 247908

DATE FILED: May 20, 1994

PARENT-CASE:  
This application is a continuation-in-part application of Ser. No.  
08/061,695 filed on May 12, 1993  
presently abandoned.

FOREIGN-APPL-PRIORITY-DATA:  
COUNTRY

APPL-NO	APPL-DATE
WO	
PCT/US94/05288	May 12, 1994

IN: Celeste; Anthony J., Wozney; John M.

AB: Purified Bone Morphogenetic Protein-10 proteins and processes for producing them are disclosed. Recombinant DNA molecules encoding the BMP-10 proteins are also disclosed. The proteins may be used in the treatment of bone and cartilage defects and in wound healing and related tissue repair.

L7: Entry 39 of 46

File: USPT  
Jun 10, 1997

DOCUMENT-IDENTIFIER: US 5637480 A  
TITLE: DNA molecules encoding bone morphogenetic protein-10

DEPR:  
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

40. Document ID: US 5635372 A

L7: Entry 40 of 46  
File: USPT  
Jun 3, 1997

US-PAT-NO: 5635372  
DOCUMENT-IDENTIFIER: US 5635372 A  
TITLE: BMP-15 compositions  
DATE-ISSUED: June 3, 1997

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 435/358, 435/360, 536/23.4, 536/23.5

APPL-NO: 8/ 446924  
DATE FILED: May 18, 1995

IN: Celeste; Anthony J., Dube; Jennifer L., Lyons; Karen M., Hogan; Brigid

AB: Purified BMP-15-related proteins and processes for producing them are disclosed. DNA molecules encoding the BMP-15-related proteins are also disclosed. The proteins may be used in the treatment of bone and cartilage and/or other connective tissue defects and in wound healing and related tissue repair.

L7: Entry 40 of 46  
File: USPT  
Jun 3, 1997

DOCUMENT-IDENTIFIER: US 5635372 A  
TITLE: BMP-15 compositions

DEPR:  
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

41. Document ID: US 5399677 A

L7: Entry 41 of 46  
File: USPT  
Mar 21, 1995

US-PAT-NO: 5399677  
DOCUMENT-IDENTIFIER: US 5399677 A  
TITLE: Mutants of bone morphogenetic proteins  
DATE-ISSUED: March 21, 1995

US-CL-CURRENT: 536/23.5; 530/350, 530/399, 536/23.51

APPL-NO: 8/ 163877  
DATE FILED: December 7, 1993

IN: Wolfman; Neil M., McCoy; John



AB: DNA molecules encoding mutant forms of bone morphogenetic proteins (BMP) are disclosed. The mutant forms of BMP can be produced bacterially and refolded to produce biologically active homodimers or heterodimers of BMP. A method of making such mutant BMPs is also disclosed.

L7: Entry 41 of 46

File: USPT

Mar 21, 1995

DOCUMENT-IDENTIFIER: US 5399677 A  
TITLE: Mutants of bone morphogenetic proteins

DEPR:

The in vitro biological activity of the refolded bone morphogenetic proteins is monitored by the

W-20 assay as set forth in Example 9. Use of the W-20-17 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with

BMP [R. S. Thies et al., Journal of Bone and Mineral Research 5(2):305 (1990); and R. S. Thies et al., Endocrinology 130:1318-1324 (1992)]. W-20-17 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital,

Boston, Mass. Treatment of W-20-17 cells with BMP results in (1) increased alkaline phosphatase production, (2) induction of parathyroid hormone stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date the conversion of W-20-17 stromal cells to osteoblast-like cells

has been observed only upon treatment with bone morphogenetic proteins. The in vivo biological

activity of the refolded bone morphogenetic proteins is monitored by a modified version of the rat bone formation assay described in Sampath and Reddi, Proc. Natl. Acad. Sci. USA, 80:6591-6595 (1983)

herein called the Rosenmodified Sampath-Reddi assay, as set forth in Example 10.

AB: A composition is disclosed comprising a pharmaceutically acceptable admixture of an osteogenic protein; a porous particulate polymer matrix; an osteogenic protein-sequestering amount of blood clot; and a calcium sulfate hemihydrate-containing substance. Also disclosed are formulations of bone morphogenetic proteins with improved solubility and/or stability characteristics.

L7: Entry 42 of 46

File: USPT

Jan 31, 1995

DOCUMENT-IDENTIFIER: US 5385887 A  
TITLE: Formulations for delivery of osteogenic proteins

DEPR:

Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of

Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].

Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by

researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20

cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)

induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)

and (2) represent characteristics associated with the osteoblast phenotype, the ability to

synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,

to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon

treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells

correlate with the in vivo bone forming activity known for BMPs.

43. Document ID: WO 9833515 A1

L7: Entry 43 of 46

File: EPAB

Aug 6, 1998

42. Document ID: US 5385887 A

L7: Entry 42 of 46

File: USPT

Jan 31, 1995

US-PAT-NO: 5385887  
DOCUMENT-IDENTIFIER: US 5385887 A  
TITLE: Formulations for delivery of osteogenic proteins  
DATE-ISSUED: January 31, 1995

US-CL-CURRENT: 514/12; 106/645, 424/423, 424/426, 514/21, 514/8, 530/350, 530/397, 530/399, 530/840

APPL-NO: 8/ 119772  
DATE FILED: September 10, 1993

IN: Yim; Calvin W. K., Huberty; Michael C., Northey, Jr.; Richard P., Schrier; Jay A.

PUB-NO: WO009833515A1  
DOCUMENT-IDENTIFIER: WO 9833515 A1  
TITLE: STIMULATORY EFFECTS OF bFGF AND BMP-2 ON OSTEOGENIC DIFFERENTIATION OF MESENCHYMAL STEM CELLS

PUBN-DATE: August 6, 1998

INT-CL (IPC): A61K 38/18; C07K 14/50; C07K 14/51; C12N 5/06  
EUR-CL (EPC): A61K038/18; C12N005/06

APPL-NO: US09802143  
APPL-DATE: February 4, 1998

PRIORITY-DATA: US03711997P (February 5, 1997)

IN: DENNIS, JAMES E, CAPLAN, ARNOLD I

AB: CHG DATE=19990617 STATUS=O>Bone marrow stroma

contains multipotential mesenchymal progenitor cells which can differentiate into osteoblastic cells; we refer to these cells as mesenchymal stem cells (MSCs). Basic fibroblast growth factor (bFGF) and bone morphogenetic protein-2(BMP-2), have been implicated in the osteogenic regulatory process by virtue of their mitogenic and differentiation activities, respectively. This study examines and compares the effects of bFGF and BMP-2 on dexamethasone (Dex)-dependent in vitro osteogenic differentiation of rat marrow-derived MSCs. A 6-day exposure to bFGF markedly stimulated cell growth and induced osteoblastic differentiation as shown by osteocalcin mRNA expression (day 14), bone nodule formation (day 18), and calcium deposition (day 18). These results indicate that bFGF enhances both mitogenic activity and osteogenic development of Dex-treated marrow MSCs. In contrast, BMP-2 did not induce an osteogenesis as strongly as bFGF. Thus, exposure to BMP-2 slightly increased bone nodule number and calcium content compared with the control. Exposure of MSCs to both BMP-2 and bFGF induced expression of osteocalcin mRNA and mineralizing bone-like nodules as early as day 11, and resulted in enhancement of bone formation more markedly than either factor alone. Consistent with these results, porous calcium phosphate ceramic cubes implanted in vitro, which were loaded with MSCs pre-exposed to both bFGF and BMP-2, showed higher histologic score for bone formation than those with MSCs pre-exposed to either bFGF or BMP-2. These data indicate that combined treatment with bFGF or BMP-2 synergistically enhances the osteogenic potency of bFGF in rat marrow MSC culture.

L7: Entry 43 of 46

File: EPAB

Aug 6, 1998

DOCUMENT-IDENTIFIER: WO 9833515 A1  
TITLE: STIMULATORY EFFECTS OF bFGF AND BMP-2 ON OSTEOGENIC DIFFERENTIATION OF MESENCHYMAL STEM CELLS

44. Document ID: WO 200005344 A1, AU 9951242 A, EP 1100872 A1

L7: Entry 44 of 46

File: DWPI

Feb 3, 2000

DERWENT-ACC-NO: 2000-171427  
DERWENT-WEEK: 200015  
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TITLE: Maintaining Drosophila germline stem cells, useful for developing methods for treating e.g. tumors, infertility, hematologic conditions, wounds, aging or damaged or diseased tissues

PRIORITY-DATA: 1998US-094008P (July 24, 1998)

PATENT-FAMILY:  
PUB-NO

PUB-DATE

LANGUAGE  
PAGES  
MAIN-IPC

WO 200005344 A1	February 3, 2000	E	040	C12N005/02
AU 9951242 A	February 14, 2000		000	C12N005/02
EP 1100872 A1	May 23, 2001	E	000	C12N005/02

APPLICATION-DATA:  
PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

WO 200005344A1	July 23, 1999	1999WO-US16633	
AU 9951242A	July 23, 1999	1999AU-0051242	
AU 9951242A		WO 200005344	Based on
EP 1100872A1	July 23, 1999	1999EP-0935857	
EP 1100872A1	July 23, 1999	1999WO-US16633	
EP 1100872A1		WO 200005344	Based on

INT-CL (IPC): C12N 5/02; C12N 5/06

IN: SPRADLING, A C, XIE, T

AB: NOVELTY - A method for maintaining germline stem cells of Drosophila comprises providing a population of the germline stem cells, and stimulating signal transduction by a bone morphogenic protein (BMP) signaling pathway in at least one cell of the population, the stimulation maintains more germline stem cells in the population compared to a population which has not had the signal transduction., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:, (1) a cell population made by the novel method, where there are at least 10 germline stem cells in the population for each germline stem cell present prior to stimulation of BMP signaling;, (2) a method for maintaining Drosophila stem cells comprising providing a population comprised of the stem cells, and stimulating decapentaplegic (dpp) signaling such that more stem cells of the population are maintained as at least viable or undifferentiated as compared to a population of stem cells which has not been stimulated;,, (3) a method of reducing or eliminating stem cells or tumor cells of an organism comprising regressing signal transduction by a BMP receptor pathway such that the stem cells or tumor cells are reduced or eliminated;,, (4) a method of increasing abundance of stem cells of an organism comprising stimulating signal transduction by a BMP receptor pathway such that

abundance of at least some stem cells is increased; (5) a method of increasing lifetime of stem cells of an organism comprising stimulating signal transduction by a BMP receptor pathway such that the lifetime of at least some stem cells is increased., ACTIVITY - Vulnery; cytostatic., MECHANISM OF ACTION - Bone morphogenetic protein modulator., USE - The methods can be used for maintaining or propagating Drosophila stem cells in vivo or in vitro. Using the methods, it is possible to extend the life span of stem cells. Drugs that upregulate BMP signaling to stem cells may enhance fertility in humans and animals, such as male fertility in patients with reduced numbers of germline stem cells (basal cells). Such drugs may ameliorate hematologic conditions caused by reduced stem cell functioning, e.g. aplastic anemias, agammaglobulinemia, and related conditions. Drugs enhancing BMP signaling may enhance wound healing. Aging-related pathologies caused by loss of stem cells, such as hair loss, loss of muscle mass, reduction of blood cell numbers, and the aging of the skin and other stem cell-dependent tissues could be treated by increasing BMP signal transduction. Compounds enhancing BMP signaling may increase the average lifespan of an organism. Drugs inhibiting BMP signaling pathways may be useful therapies against teratocarcinoma by causing stem cell differentiation, e.g. drugs which inhibit BMP signaling may be successful treatments against ovarian germline tumors dependent upon BMP signaling for continued growth. Increased or decreased BMP signaling to stem cells might allow populations of stem cells to expand prior to bone marrow transplant, increasing the chances of successful transplantation and reducing the amount of donor marrow required. Further, control of BMP signaling pathways may permit stem cells other than those in bone marrow to be removed from a patient, expanded in vitro, and subsequently reintroduced into the patient to repair tissues damaged by injury or disease, such as Parkinson's disease. Bone marrow from patients with hematologic tumors, such as lymphoma and leukemia, could be tested for BMP sensitivity. Positive test results for BMP sensitivity would allow steps to be taken to avoid potential side effects of anti-BMP treatment in vivo, e.g. marrow removed from the patient could be cleansed of tumor cells by inhibiting BMP signaling, thereby inducing differentiation of tumor cells and reducing the tumor burden. The cleansed marrow would subsequently be returned to the patient in an autologous bone marrow transplant. Such differentiation therapy could also be used for solid tumors e.g. sarcoma, carcinoma, and neuroglioma to reduce tumor burden. Therapy may be used alone or in association with other treatments e.g. chemotherapy, hyperthermia, or radiation, which preferentially kills rapidly dividing cells and surgical resection of tumor. The methods can provide a model of ovarian tumor formation in which overexpression of dpp produces ovarian stem cell tumors. In addition, one or more genes of the stem cell may be activated or inhibited by chemical or environmental induction, antisense, ribozyme, chimeric repair vector, RNAi, or random/sequence-specific insertion. Ectopic expression of a gene may be controlled in a particular spatial or temporal manner, mimic pathologic or disease states, or create phenocopies of mutations in the endogenous gene. The methods can also be used in agriculture and wildlife conservation.

L7: Entry 44 of 46

File: DWPI

Feb 3, 2000

DERWENT-ACC-NO: 2000-171427  
DERWENT-WEEK: 200015  
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TITLE: Maintaining Drosophila germline stem cells, useful for developing methods for treating e.g. tumors, infertility, hematologic conditions, wounds, aging or damaged or diseased tissues

ABTX:  
NOVELTY - A method for maintaining germline stem cells of Drosophila comprises providing a population of the germline stem cells, and stimulating signal transduction by a bone morphogenic protein (BMP) signaling pathway in at least one cell of the population, the stimulation maintains more germline stem cells in the population compared to a population which has not had the signal transduction.

ABTX:  
(1) a cell population made by the novel method, where there are at least 10 germline stem cells in the population for each germline stem cell present prior to stimulation of BMP signaling;

ABTX:  
(3) a method of reducing or eliminating stem cells or tumor cells of an organism comprising regressing signal transduction by a BMP receptor pathway such that the stem cells or tumor cells are reduced or eliminated;

ABTX:  
(4) a method of increasing abundance of stem cells of an organism comprising stimulating signal transduction by a BMP receptor pathway such that abundance of at least some stem cells is increased;

ABTX:  
(5) a method of increasing lifetime of stem cells of an organism comprising stimulating signal transduction by a BMP receptor pathway such that the lifetime of at least some stem cells is increased.

ABTX:  
USE - The methods can be used for maintaining or propagating Drosophila stem cells in vivo or in vitro. Using the methods, it is possible to extend the life span of stem cells. Drugs that upregulate BMP signaling to stem cells may enhance fertility in humans and animals, such as male fertility in patients with reduced numbers of germline stem cells (basal cells). Such drugs may ameliorate hematologic conditions caused by reduced stem cell functioning, e.g. aplastic anemias, agammaglobulinemia, and related conditions. Drugs enhancing BMP signaling may enhance wound healing. Aging-related pathologies caused by loss of stem cells, such as hair loss, loss of muscle mass, reduction of blood cell numbers, and the aging of the skin and other stem cell-dependent tissues could be treated by increasing BMP signal transduction. Compounds enhancing BMP signaling may increase the average lifespan of an organism. Drugs inhibiting BMP signaling pathways may be useful therapies against teratocarcinoma by causing stem cell differentiation, e.g. drugs which inhibit BMP signaling may be successful treatments against ovarian germline tumors dependent upon BMP signaling for continued growth. Increased or decreased BMP signaling to stem cells

might allow populations of stem cells to expand prior to bone marrow transplant, increasing the chances of successful transplantation and reducing the amount of donor marrow required. Further, control of BMP signaling pathways may permit stem cells other than those in bone marrow to be removed from a patient, expanded in vitro, and subsequently reintroduced into the patient to repair tissues damaged by injury or disease, such as Parkinson's disease. Bone marrow from patients with hematologic tumors, such as lymphoma and leukemia, could be tested for BMP sensitivity. Positive test results for BMP sensitivity would allow steps to be taken to avoid potential side effects of anti-BMP treatment in vivo, e.g. marrow removed from the patient could be cleansed of tumor cells by inhibiting BMP signaling, thereby inducing differentiation of tumor cells and reducing the tumor burden. The cleansed marrow would subsequently be returned to the patient in an autologous bone marrow transplant. Such differentiation therapy could also be used for solid tumors e.g. sarcoma, carcinoma, and neuroglioma to reduce tumor burden. Therapy may be used alone or in association with other treatments e.g. chemotherapy, hyperthermia, or radiation, which preferentially kills rapidly dividing cells and surgical resection of tumor. The methods can provide a model of ovarian tumor formation in which overexpression of dpp produces ovarian stem cell tumors. In addition, one or more genes of the stem cell may be activated or inhibited by chemical or environmental induction, antisense, ribozyme, chimeric repair vector, RNAi, or random/sequence-specific insertion. Ectopic expression of a gene may be controlled in a particular spatial or temporal manner, mimic pathologic or disease states, or create phenocopies of mutations in the endogenous gene. The methods can also be used in agriculture and wildlife conservation.

45. Document ID: EP 1037907 A2, WO 9929718 A2, AU 9914631 A, US 6027917 A

L7: Entry 45 of 46

File: DWPI

Sep 27, 2000

DERWENT-ACC-NO: 1999-385570  
DERWENT-WEEK: 200048  
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TITLE: New Purified bone morphogenic protein-17 and -18 (BMP-17 and BMP-18) polypeptides, useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells

PRIORITY-DATA: 1997US-0987904 (December 10, 1997)

PATENT-FAMILY:

PUB-NO

PUB-DATE

LANGUAGE

PAGES

MAIN-IPC

EP 1037907 A2

September 27, 2000

E

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C07K014/00

WO 9929718 A2  
June 17, 1999

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C07K014/00

AU 9914631 A

June 28, 1999

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C07K014/00

US 6027917 A

February 22, 2000

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C12N001/21

APPLICATION-DATA:

PUB-NO

APPL-DATE

APPL-NO

DESCRIPTOR

EP 1037907A2

November 17, 1998

1998EP-0958631

EP 1037907A2

November 17, 1998

1998WO-US24613

EP 1037907A2

WO 9929718

Based on

WO 9929718A2

November 17, 1998

1998WO-US24613

AU 9914631A

November 17, 1998

1999AU-0014631

AU 9914631A

WO 9929718

Based on

US 6027917A

December 10, 1997

1997US-0987904

INT-CL (IPC): C07K 14/00; C12N 1/21; C12N 5/10; C12N 15/12; C12N 15/63

IN: CELESTE, A J, MURRAY, B L

AB: NOVELTY - Purified bone morphogenic protein (BMP) polypeptides (I), comprising amino acids 1-224 (BMP-17) or amino acids 1-231 (BMP-18) from fully defined 366 amino acid proteins given in the specification., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an isolated DNA molecule (II) comprising a DNA sequence selected from: (a) nucleotides 1, 232, 406, 427, 751 or 796 to 1059 or 1098 of fully defined 1101 cDNA sequences given in the specification; (b) nucleotides encoding amino acids -142, -65, -7, 1, 109 or 124 to 211 or 224 of BMP-17; (c) nucleotides encoding amino acids -135, -58, 1, 8, 116 or 131 to 218 or 231 of BMP-18; and (d) naturally occurring human allelic sequences and equivalent degenerative codon sequences of (a)-(c); (2) a host cell transformed with (II); (3) a vector comprising (II) in operative association with an expression control sequence; (4) a host cell transformed with (3); (5) preparation of (I); (6) a chimeric DNA molecule comprising a DNA sequence encoding a propeptide from a member of the TGF- beta superfamily of proteins linked in frame to a DNA sequence encoding BMP-17 or BMP-18 comprising amino acids 1-224 of the 366 sequence given in the specification; and (7) antibodies to BMP-17 and BMP-18., ACTIVITY - BMP-17 and BMP-18 stimulate FSH., USE - (I) is useful for the induction of growth and/or

differentiation of undifferentiated embryonic and stem cells, and for the treatment of bone, cartilage and other connective tissue defects including tendons, ligaments and meniscus, in wound healing and related tissue repair, and for treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney tissue., DNA (II) is useful as probes to detect expression of (I), and the vectors are useful for delivery of (I) to cells of a patient., NOVELTY - Purified bone morphogenic protein (BMP) polypeptides (I), comprising amino acids 1-224 (BMP-17) or amino acids 1-231 (BMP-18) from fully defined 366 amino acid proteins given in the specification., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:, (1) an isolated DNA molecule (II) comprising a DNA sequence selected from:, (a) nucleotides 1, 232, 406, 427, 751 or 796 to 1059 or 1098 of fully defined 1101 cDNA sequences given in the specification:, (b) nucleotides encoding amino acids -142, -65, -7, 1, 109 or 124 to 211 or 224 of BMP-17:, (c) nucleotides encoding amino acids -135, -58, 1, 8, 116 or 131 to 218 or 231 of BMP-18; and, (d) naturally occurring human allelic sequences and equivalent degenerative codon sequences of (a)-(c);, (2) a host cell transformed with (II);, (3) a vector comprising (II) in operative association with an expression control sequence:, (4) a host cell transformed with (3);, (5) preparation of (I);, (6) a chimeric DNA molecule comprising a DNA sequence encoding a propeptide from a member of the TGF- beta superfamily of proteins linked in frame to a DNA sequence encoding BMP-17 or BMP-18 comprising amino acids 1-224 of the 366 sequence given in the specification; and, (7) antibodies to BMP-17 and BMP-18., ACTIVITY - BMP-17 and BMP-18 stimulate FSH., USE - (I) is useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells, and for the treatment of bone, cartilage and other connective tissue defects including tendons, ligaments and meniscus, in wound healing and related tissue repair, and for treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds, and organs such as liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney tissue., DNA (II) is useful as probes to detect expression of (I), and the vectors are useful for delivery of (I) to cells of a patient.

L7: Entry 45 of 46

File: DWPI

Sep 27, 2000

DERWENT-ACC-NO: 1999-385570  
DERWENT-WEEK: 200048  
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TITLE: New Purified bone morphogenic protein-17 and -18 (BMP-17 and BMP-18) polypeptides, useful for the induction of growth and/or differentiation of undifferentiated embryonic and stem cells

46. Document ID: WO 9835022 A1, AU 9861444 A

L7: Entry 46 of 46

File: DWPI

Aug 13, 1998

DERWENT-ACC-NO: 1998-447219  
DERWENT-WEEK: 199838  
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TITLE: Distinguishing between undifferentiated and differentiated mesenchymal stem cells - from relative expression of p21CIP1, also indentifying inducers of these cells, cell competence and agents that induce expression of bone morphogenic protein receptors

PRIORITY-DATA: 1997US-036917P (February 6, 1997)

PATENT-FAMILY:  
PUB-NO

PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9835022 A1	August 13, 1998	E	031
AU 9861444 A	August 26, 1998	000	C12N005/08

APPLICATION-DATA:  
PUB-NO

APPL-DATE	APPL-NO	DESCRIPTOR
WO 9835022A1	February 5, 1998	1998WO-US02137
AU 9861444A	February 5, 1998	1998AU-0061444
AU 9861444A	WO 9835022	Based on

INT-CL (IPC): C07K 14/495; C07K 14/51; C12N 5/08

IN: CONNOLLY, T J

AB: Undifferentiated human mesenchymal stem cells (A) are distinguished from corresponding (partially) differentiated cells (B) by measuring upregulation of p21CIP1 (a cyclin inhibitor protein) expression in (B). Also new are: (1) identifying an inducer (I) of mesenchymal stem cell lineage by exposing (A) to test compound and measuring any upregulation of p21CIP1 expression; (2) determining ability of progenitor cells to differentiate by measuring upregulation of p21CIP1, and (3) method for identifying an agent (II) that induces (A) to express receptors for bone morphogenic protein (BMP)., The cells are modified with a genetic construct encoding a marker protein, especially luciferase, DNA under control of a p21CIP1 promoter, and the level of reporter expression is correlated with p21CIP1 activity. Alternatively, the level of constitutive expression is measured using a labelled anti-p21CIP1 antibody. (I) are growth factors, specifically BMP. Method (3) is based

on the observation that

co-expression of type I and II BMP receptors in (A) stimulates p21CIP1 transcription., USE -

The methods are used (i) for quality control to ensure that cells are really undifferentiated

and (ii) to determine competence for differentiation, particularly where intended for in vivo

tissue (bone) repair. Agents that induce high levels of p21CIP1 are potential antineoplastic

agents.

L7: Entry 46 of 46

File: DWPI

Aug 13, 1998

DERWENT-ACC-NO: 1998-447219

DERWENT-WEEK: 199838

COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Distinguishing between undifferentiated and differentiated mesenchymal stem cells - from relative expression of p21CIP1, also indentifying inducers of these cells, cell competence and agents that induce expression of bone morphogenic protein receptors

ABTX:

Undiffer entiated human mesenchymal stem cells (A) are distinguished from corresponding (partially)

differentiated cells (B) by measuring upregulation of p21CIP1 (a cyclin inhibitor protein)

expression in (B). Also new are: (1) identifying an inducer (I) of mesenchymal stem cell lineage by

exposing (A) to test compound and measuring any upregulation of p21CIP1 expression; (2) determining

ability of progenitor cells to differentiate by measuring upregulation of p21CIP1, and (3) method

for identifying an agent (II) that induces (A) to express receptors for bone morphogenic protein

(BMP).